EXHIBIT 85

84-224

Environmental Protection Agency
Health Effects Update

William J. Nicholson, Ph.D.

Environmental Sciences Laboratory
Department of Community Medicine
Mount Sinai School of Medicine of
The City University of New York
New York, New York 10029

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Table of Contents

1. SUMMARY

Data developed in the past decade have added much to our knowledge of asbestos disease as the results of studies of large populations with long follow-up have become available. As has long been known, lung cancer and mesothelioma are the most important asbestos-related causes of death among exposed individuals. Cancer at other sites has also been associated with asbestos exposure in some studies. Statistically significant excesses have been associated with asbestos exposure for cancers of the larynx, esophagus, stomach, colon-rectum, kidney and ovary. As a group, all other malignancies are significantly elevated in some studies, but small numbers present significance from being achieved at any one site. The strength and consistency of the evidence for cancers at these other sites is less than for bronchogenic carcinoma or mesothelioma. Nevertheless, gastrointestinal cancer is generally found to be elevated in studies demonstrating a high lung cancer risk with the excess GI risk correlating with the excess lung cancer risk.

Data from the large study of insulators allow models to be developed for the time and age dependence of lung cancer and mesothelioma risk. Other studies have provided exposure-response information. The accumulated data suggest that the excess risk of lung cancer from asbestos exposure is proportional to the cumulative exposure (the duration times the intensity) and the underlying risk of lung cancer in the absence of exposure. The time course of lung cancer is largely determined by the time course of the underlying risk. The risk of death from mesothelioma, on the other hand, increases very rapidly with time from onset of exposure. The risk is independent of age and of other factors, such as cigarette smoking. As with lung cancer, the risk appears to be proportional to the cumulative exposure of asbestos in a given period. The dose and time relationships for other asbestos cancers are uncertain.

Eleven studies allow estimates to be made of the fractional increased risk of lung cancer per unit exposure. The values obtained from different studies vary widely but a range of fractional unit risks can be specified that encompass the results of most studies. Similar variability exists in

the unit exposure risks developed for the observed incidence of mesothelioma in four studies.

The variability in the units risks cannot be attributed to differences in exposures to different fiber types. All major commercial asbestos varieties (chrysotile, amosite and crocidolite) appear equally capable of producing pleural mesothelioma and lung cancer. Peritoneal mesothelioma appears to be associated with exposure to amphibole asbestos rather than chrysotile, but this suggestions is tempered by the possibility of severe misdiagnosis of the disease.

Animal studies confirm the human epidemiological results. All major asbestos varieties produce lung cancer and mesothelioma with no identifiable difference in carcinogenic potency. Implantation and injection studies show that fiber dimensionality, and not chemistry is the most important factor in fiber-induced carcinogenicity. Long (> 4 μm) and thin (≤ 4 μm) fibers are the most carcinogenic when in place at a cancer inducible site. However, the size dependence of the deposition and migration of fibers also affects their carcinogenic action.

Measurements exist that demonstrate significant asbestos exposure, exceeding 100 times background, occurs to individuals in other than occupational circumstances. Currently, the most important of these exposures is from the release of fibers from asbestos-containing surfacing materials in schools, auditoriums and other public buildings or from asbestos sprayed fireproofing in high rise office buildings. The potential is high for future exposure from the maintenance, repair, and removal of these materials and previously applied as thermal insulation.

Extrapolations of risks of asbestos cancers from occupational circumstances can be made, although any numerical estimates have a large (approximately ten-fold) uncertainty.

2. INTRODUCTION

The specific purpose of this health effects review is to evaluate the information relating to human disease from asbestos-exposure that has been developed since 1972. The review will be used to ascertain whether the substantial amount of new research that has been reported in the last decade warrants reconsideration or revision of the standard published by the Environmental Protection Agency for asbestos emissions. Thus, emphasis will be placed on the literature published subsequent to 1972 and on those papers that would provide information on the risk from low-level exposures such as might be encountered in the non-occupational environment. Specifically, this report will address the following issues:

1. Are there satisfactory models for the age, time and exposure-dependence of asbestos diseases that can be utilized in a quantitative risk assessment?

2. Is there consistency among studies and sufficiently good estimates of exposure in occupational circumstances so that useful exposure-response relationships can be established?

3. Do these studies indicate any significant differences in the carcinogenic potency of the different asbestos minerals, or of fibers of different dimensionality?

4. What additional or confirmatory information relating to human carcinogenicity in provided by animal studies?

5. What are the non-occupational concentrations of asbestos to which populations are exposed?

6. Is there a basis for estimating numerical risks of asbestos disease in environmental exposure circumstances?

Two documents provide a good review of the status of knowledge of the health effects of asbestos in the early 1970s. One is the criteria document for occupational exposure to asbestos produced by the National Institute of Occupational Safety and Health as part of the Occupational Safety and Health Administration's consideration of an asbestos standard in early 1972 (NIOSH, 1972). The second is the proceedings of a conference sponsored by the International Agency for Research on Cancer (IARC) which was convened in October, 1972 with the stated purpose of reviewing the knowledge of the biological effects of asbestos at that time (IARC, 1973). This latter document included a report by an Advisory Committee on Asbestos Cancers appointed by the IARC to review evidence relating exposures to asbestos dust to cancers.

2.1 Summary of asbestos health effects through 1972

This summary will rely heavily on review articles in the proceedings of the October, 1972 IARC meeting and in the report of the IARC Advisory Committee published therein (IARC, 1973)for the summary of health effects knowledge in 1973. No health effects review was undertaken by the EPA at the time of promulgation of the 1973 Emission Standard (EPA, 1973).

2.1.1 Occupational exposure

Diseases considered to be associated with asbestos exposure in 1972 included asbestosis, mesothelioma, bronchogenic carcinoma, and cancers of the gastrointestinal tract, including the esophagus, stomach, colon, and rectum. Lung cancer was associated with exposure to all principal commercial varieties of asbestos fiber, amosite, anthophyllite, crocidolite and chrysotile. Excess risks of bronchogenic carcinoma were documented in mining and milling, manufacturing, and end product use (application of insulation materials). Mesothelioma was a common cause of death among factory employees, insulation applicators, and workmen employed in the mining and milling of crocidolite. A much lower risk of death from mesothelioma was observed among chrysotile or

amosite mine and mill employees and no cases were associated with anthophyllite exposure. It was suggested by the IARC Advisory Committee that the risk of death from mesothelioma was greatest with crocidolite, less with amosite and apparently still less with chrysotile. This suggestion was based on associations of disease with exposures. No unit exposure risk information existed.

Information on exposure-response relationships lung cancer risk among various exposed groups was scanty. Data from Canadian mine and mill employees clearly indicated an increasing risk with increasing exposure measured in terms of millions of particles per cubic foot-years (mppcf-y), but data on the risk at minimal exposure was uncertain as expected deaths calculated using adjacent county rates suggested all exposure categories were at elevated risk (McDonald et al. 1974). A study of retirees of the largest U.S. asbestos manufacturer showed lung cancer risks ranging from 1.7 times that expected in the lowest exposure category to 5.6 times expected in the highest (Enterline et al. 1973). Again, exposures were expressed in mppcf-y and information on conversion of mppcf to f/ml was only available for textile production. Despite the paucity of data, the report of the Advisory Committee on Asbestos Cancers to the IARC (1973) stated "The evidence .... suggests that an excess lung carcinoma risk is not detectable when the occupational exposure has been low. These low occupational exposures have almost certainly been much greater than that to the public from general air pollution." Limited data existed on the association of gastrointestinal cancer with asbestos exposure, but the "excess is relatively small compared with that for bronchial cancer."

The prevalence of asbestosis, particularly as manifest by X-ray abnormalities of the pleura or parenchymal tissue, had more extensive documentation than the risk of the asbestos-related malignancies. This, in part, was the result of knowledge of this disease extending back to the turn of the century, whereas the

malignant potential of asbestos was not suggested until 1935 (Lynch and Smith, 1935; Gloyne, 1936) and not widely appreciated until the 1940s (Merewether, 1947). Such asbestosis had been documented in a wide variety of work circumstances and associated with all commercial types of asbestos fiber. Among some exposed groups, 50% to 80% of individuals employed for 20 or more years were found to have abnormal x-rays characteristic of asbestos exposure (Selikoff et al., 1965; Lewinsohn, 1972). Data supplied to the British Occupational Hygiene Society (BOHS, 1968) by the medical director of a large textile production facility in Great Britain were analyzed by Berry (1973) in terms of a fiber exposure-response relationship. The results were utilized in establishing the 1969 British regulation on asbestos. These data are shown in Figure 2-1, and suggested that the risk of developing the earliest signs of asbestosis (rales) was less than 1% for accumulated fiber exposure of 100 f-yr/ml (e.g., 2 f/ml for 50 years). However, shortly after the establishment of the British Standard, additional data from the same factory population suggested a much greater prevalance of X-ray abnormalities than was believed to exist at the time the British Standard was set (Lewinsohn, 1972). This was in part the result of the use of the new ILO U/C standard classification of X-rays (ILO, 1971) and in part the result of a longer time from onset of employment. As the progression of asbestosis depends on both cumulative exposure and time from exposure, analysis in terms of only one variable (as in Figure 2-1) can be misleading.

2.1.2 Environmental and indirect occupational exposure circumstances.

Four research groups had shown that asbestos disease risk could exist in other than direct occupational circumstances. In 1960, Wagner, Sleggs and Marchand (1960) showed that a mesothelioma risk in environmental circumstances existed in the mining areas of the Northwest Cape Province of South Africa. Of 33 mesothelioma reported over a five year period, roughly half were from

Figure 2-1

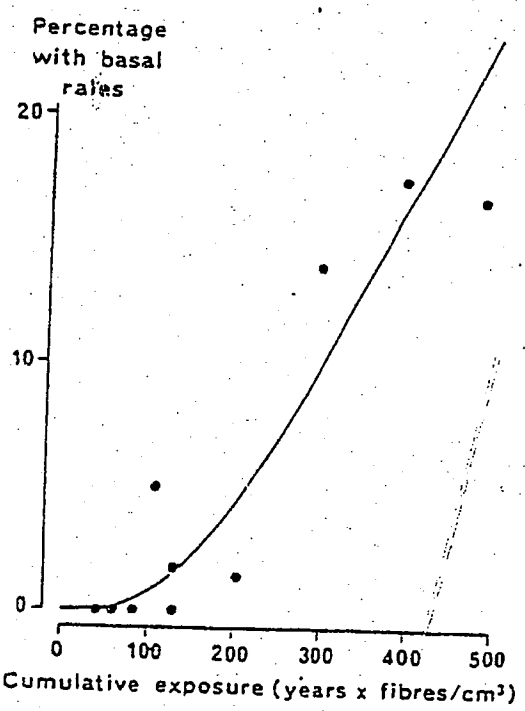

Fig. 2-1 Dose-response relationship for prevalance of basal rales in a chrysotile asbestos factory

occupational exposure. All but one of the remainder, however, were from exposure occasioned by living or working in the area of the mining activity. A second study showing an extra-occupational risk was that of Newhouse and Thomson (1965) who investigated the occupational and residential background of 76 individuals deceased of mesothelioma in the London hospital. Forty-five of the decedents had been employed in an asbestos industry; of the remaining 31, 9 lived with someone employed in asbestos work and 11 were in individuals who resided within half a mile of an asbestos factory. Bohlig and Hain (1973) further defined the residential risk by documenting environmental asbestos exposure near a factory in 38 cases in Hamburg. The final study, and a particularly important one because of the size of the population implied to be at risk, is that of Harries (1968), who pointed to a risk of asbestos disease from indirect occupational exposure in the shipbuilding industry. He described the presence of asbestosis in 13 individuals and mesothelioma in 5 others who were employed in a shipyard, but were not members of trades that regularly used asbestos. Rather, their work took place where insulation application or removal was being done by others.

Evidence of ubiquitous general population exposure and environmental contamination from the spraying of asbestos on the steel work of high rise buildings was established by 1972. Data by Nicholson and Pundsack (1973) showed that asbestos was commonly found at concentrations of ng/m^3 in virtually all United States cities and at concentrations of µg/l in river systems of the United States. Concentrations of hundreds of ng/m^3 were documented at distances up to one quarter of a mile from fireproofing sites. Mesothelioma was acknowledged by the Advisory Committee to be associated with environmental exposures but "the evidence relates to conditions many years ago .... There is no evidence of a risk to the general public at present." Further, their report stated that, "There is at present no evidence of lung damage by asbestos to the general public," and, "Such evidence as there is does not indicate any risk" from asbestos fibers in water, beve-

rages, food or parenteral drugs. No mention was made in the report of risks from indirect occupational asbestos exposures.

2.1.3 Analytical methodology

The late 1960s and early 1970s was a period when significantly improved methods were developed for assessing asbestos disease and the quantifying of asbestos in the environment. In 1971, a standardized methodology was established for the identification of pneumoconiosis, the ILO U/C Classification of Pneumoconioses (ILO, 1971). This allowed a uniform criteria to be utilized in assessing the prevalence of asbestos-related X-ray abnormalities. Further, significant advances were achieved in the quantification of asbestos aerosols. In the late 1960s, the membrane filter technique was developed for the measurement of asbestos fibers in workplace aerosols. While having some limitations, the procedure established a standardized method, using simple instrumentation, that was far superior to any that existed previously. This would subsequently allow epidemiological studies to base exposure estimates on a standardized criterion. Additionally, experimental techniques in the quantification of asbestos at concentrations of tenths of ng/cm of air and tenths of µg/l of water were developed. This extended the sensitivity of exposure estimates approximately three orders below those of occupational aerosols and allowed assessment of general population exposures. Finally, techniques for the analysis of asbestos in lung and other body tissues were developed. Both digestion techniques, with electronmicroscopic analysis of fibers contained in the digest, and the electronmicroscopic analysis of thin sections of lung tissue showed asbestos fibers to be commonly present in the lung tissue of general population residents, as well as in that of individuals exposed in occupational circumstances.

2.1.4 Animal Studies

Experimental animal studies using asbestos fibers confirmed the risks of lung cancer and mesothelioma from amosite, crocidolite and chrysotile. In each case, the establishment of a risk in animals followed the association of the malignancy with a human exposure. Lung cancer, for example, being suggested as causally related to asbestos exposure in humans in 1935, but was not described in the open literature in animals until 1967 (Gross et al. 1967). Mesothelioma, reported in an asbestos worker in 1953 (Weiss, 1953), was produced in animal experimentation in 1965 (Smith, 1965). Other animal experimentation showed that combinations of asbestos and other carcinogenic materials produced an enhanced risk of asbestos cancer. Asbestos exposure combined with exposure to benz(a)pyrene was demonstrably more toxic than the exposure to either agent alone. Additionally, some materials, organic and metal compounds associated with asbestos fibers, were ruled out as an important factor in the carcinogenicity of fibers. Lastly, animal experimentation involving the application of fibers onto the pleura of animals indicated that the important factor in the carcinogenicity was the dimensionality of the fibers rather than their chemical properties (Stanton, 1973). The greatest carcinogenicity was related to fibers less than 2.5 μm in diameter having lengths in excess of 10 μm.

2.2 Current Asbestos Standards

The current Occupational Safety and Health Administration (OSHA) standards for an 8-hour time-weighted average (TWA) occupational exposure to asbestos is 2 fibers longer than 5 microns in length per milliliter of air (2 f/ml or 2,000,000 f/m^3). Peak exposures of up to 10 f/ml are permitted for no more than 10 minutes (29 CFR 1910.001). This standard has been in effect since July 1, 1976, when it replaced an earlier one of 5 f/ml (TWA). In Great Britain, a value of 1 f/ml is now the accepted level for chrysotile. This is the result of recommendations made in 1979 (Advisory Committee, 1979a), which also

recommended a TWA of 0.5 f/ml for amosite and 0.2 f/ml for crocidolite. From 1969 to 1983, 2 f/ml (TWA) was the standard for chrysotile (BOSH, 1968). This earlier British standard, in fact, served as a guide for the OSHA standard (NIOSH, 1972).

The British standard was developed specifically to prevent asbestosis among working populations; data were felt to be lacking that would allow a determination of a standard for cancer (BOHS, 1968). Unfortunately, among occupational groups, cancer is the primary cause of excess death among workers (see Chapter 3). Three-fourths or more of asbestos-related deaths are from malignancy. This fact has led OSHA to propose a lower TWA standard to 0.5 f/ml (500,000 f/m^2) in October, 1975 (29 CFR 1910.001). The National Institute for Occupational Safety and Health, in an update of their 1972 criteria document, in anticipation of hearings on a new standard, proposed a value of 0.1 f/ml (NIOSH, 1976). In the discussion of the NIOSH proposal, it was stated that the value was selected on the basis of the practical limitations of analytical techniques using optical microscopy and that 0.1 f/ml may not necessarily protect against cancer. Recognition that no information exists that would define a threshold for asbestos carcinogenesis was also contained in the preamble to the OSHA proposal. The OSHA proposal has been withdrawn, and a new proposal is anticipated. NIOSH has reaffirmed their position on an 0.1 f/ml standard (1980).

The existing Federal standard for asbestos emissions into the environment prohibits "visible emissions" (40 FR 48291). No numerical value was specified because of difficulty in monitoring ambient air asbestos concentrations in the ambient air or in stack emissions. (Time-consuming and expensive electron microscopy is often required.) Some local governmental agencies, however, may have numerical standards (New York, 27 ng/m^3 for example).

3. HUMAN HEALTH EFFECTS ASSOCIATED WITH OCCUPATIONAL EXPOSURE TO ASBESTOS

3.1 Introduction

This review of human health effects associated with occupational exposure to asbestos is largely concerned with those studies that will allow an exposure-response relationship to be established for lung cancer and mesothelioma. While lung cancer and mesothelioma are the most dominant asbestos-related malignancies, the strength of the evidence and the relative excess of cancers at extra-thoracic sites will also be discussed. Models for assessment of the risk of lung cancer and mesothelioma will be reviewed. Unit exposure risks will be estimated from eleven studies that provide information on exposure-response relationships. These estimates will illustrate that considerable variation exists in the unit exposure risks found for mesothelioma and lung cancer in the different studies. The possible sources of these different unit risks will be considered. An important question is whether the variation is the result of methodological uncertainties (i.e., on the estimates of exposure or of the magnitude of disease) or whether differences are real and must be reconciled on the basis of the character of the exposure in terms of fiber size and chemistry.

3.2 Mortality associated with asbestos exposure

The large study of U.S. and Canadian insulators by Selikoff et al. (1979) contains the largest excess of asbestos-related deaths among any group of asbestos workers studied. Thus, it best demonstrates the full spectrum of disease from asbestos exposure. The mortality experience of 17,800 asbestos insulation workers was studied prospectively from January 1, 1967 through December 31, 1976. These workers were exposed primarily to chrysotile prior to 1940, to chrysotile and amosite from 1940 through 1965, and largely to chrysotile thereafter. No crocidolite is known to have been used in the U. S. insulation material (Selikoff et al. 1970). The workers by and large applied new insulation; removal of old materials would have constituted less than 5% of their activities.

In this group, 2,271 deaths occurred, and their analysis provides important insights into the nature of asbestos disease. Table 3-1 lists the expected and observed deaths by cause, and includes data on tumors less frequently found. Lung tumors were common and accounted for approximately 21 percent of the deaths; 8 percent were from mesothelioma of the pleura or peritoneum, and 7 percent died from asbestosis. Considering all cancers, 675 excess malignancies occurred, constituting 30 percent of all deaths. In addition to the usual asbestos malignancies - lung cancer, mesothelioma, and gastrointestinal cancer - the incidences of cancers of larynx, pharynx and buccal cavity, and kidney was significantly elevated. Other tumors were also increased, but not to a statistically significant degree for individual sites. However, these other cancers, as a group, were significantly in excess, 184 observed (using best available evidence for classification) versus 131.8 expected ($p<0.001$). Some of this excess, however, may be the result of misclassification of asbestos-related lung cancer or peritoneal mesothelioma. Rather than 184 deaths, certificate of death classification attributed 252 cancer to these other sites. Pancreatic, liver and unspecified abdominal cancers were commonly misclassified. Pancreatic and abdominal cancers were often found to be peritoneal mesotheliomas, and several liver cancers were the result of a primary malignancy in the lung. As it was not possible to review all caes, some additional misclassification may still exist. However, its magnitude would not be great compared to the remaining excess of 52 cases. The excess at extra-thoracic sites may reflect mortality from the dissemination of asbestos fibers to various organs (Langer, 1974). Alternatively, it could represent a systemic effect of asbestos, perhaps on the immune system, that leads to a general increased risk of cancer (Goldsmith, 1982).

3.2.1 Accuracy of cause of death ascertainment

Table 3-1 lists the observed deaths both according to the cause recorded on the certificate of death (DC) and according to the best evidence (BE) available from medical records, surgical specimens, and autopsy protocols. In comparing occupational

Table 3-1

Deaths among 17,800 asbestos insulation workers
in the United States and Canada
January 1, 1967 - December 31, 1976
Number of men 17,800
Man-years of observation 166,853

Underlying cause of death	Expected*	Observed (BE)	Observed (DC)	Ratio o/e (BE)	Ratio o/e (DC)
Total deaths, all causes	1658.9	2271	2271	1.37	1.37
Total cancer, all sites	319.7	995	922	3.11	2.88
Cancer of lung	105.6	486	429	4.60	4.06
Pleural mesothelioma	†	63	25	-	-
Peritoneal mesothelioma	†	112	24	-	-
Mesothelioma, n.o.s.	†	0	55	-	-
Cancer of esophagus	7.1	18	18	2.53	2.53
Cancer of stomach	14.2	22	18	1.54	1.26
Cancer of colon-rectum	38.1	59	58	1.55	1.52
Cancer of larynx	4.7	11	9	2.34	1.91
Cancer of pharynx, buccal	10.1	21	16	2.08	1.59
Cancer of kidney	8.1	19	18	2.36	2.23
All other cancer	131.8	184	252	1.40	1.91
Noninfectious pulmonary diseases, total	59.0	212	188	3.59	3.19
Asbestosis	†	168	78	-	-
All other causes	1280.2	1064	1161	0.83	0.91

From Selikoff et al. (1979a)

* Expected deaths are based upon white male age-specific U.S. death rates of the U.S. National Center for Health Studies, 1967-1976.

† Rates are not available, but these have been rare causes of death in the general population.

(BE) Best evidence. Number of deaths categorized after review of best available information (autopsy, surgical, clinical).

(DC) Number of deaths as recorded from death certificate information only.

mortality with that of the general population, one usually utilizes information as recorded on death certificates since such information, without verification, serves as the basis for "expected rates". However, since mesothelioma and asbestosis are virtually unseen in the general population, their misdiagnosis (which is common) is of little importance. In contrast, their misdiagnosis among asbestos workers can cause serious distortions in assessing mortality. Not only are asbestos-related causes understated, but others, such as pancreatic cancer, might wrongly appear to be significantly elevated (Selikoff and Seidman, 1981). While substantial differences exist in the DC and BE characterization of deaths from mesothelioma and asbestosis, the BE and DC deaths from cancer of all sites and lung cancer agree reasonably well.

As we will see, mesothelioma is best described by an absolute risk model and lung cancer by a relative risk model. Thus, risks for mesothelioma will be expressed in absolute rates (deaths/1,000 person-years, e.g.). and the best medical evidence will be used, when available, to establish the number of cases. Risks for lung cancer will be quantified by the ratio of observed to expected deaths. Here, it is expected that misclassification of lung cancer deaths would occur as frequently in asbestos workers as in the general population (in terms of the percentage of lung cancer cases). Therefore, the certificate of death cause will be used for establishing the relative risks of lung cancer in asbestos-exposed groups.

3.3 Linearity of exposure-response relationships

Some limited direct evidence for linearity of response with asbestos exposure is available from three studies that compared lung cancer mortality to the cumulative total dust exposure in asbestos workplaces (Henderson and Enterline, 1979; Liddell et al., 1977: and Dement et al., 1982). Figure 3-1 shows the exposure-response data in these studies in which the ratio of observed to expected lung cancer mortal-

Figure 3-1

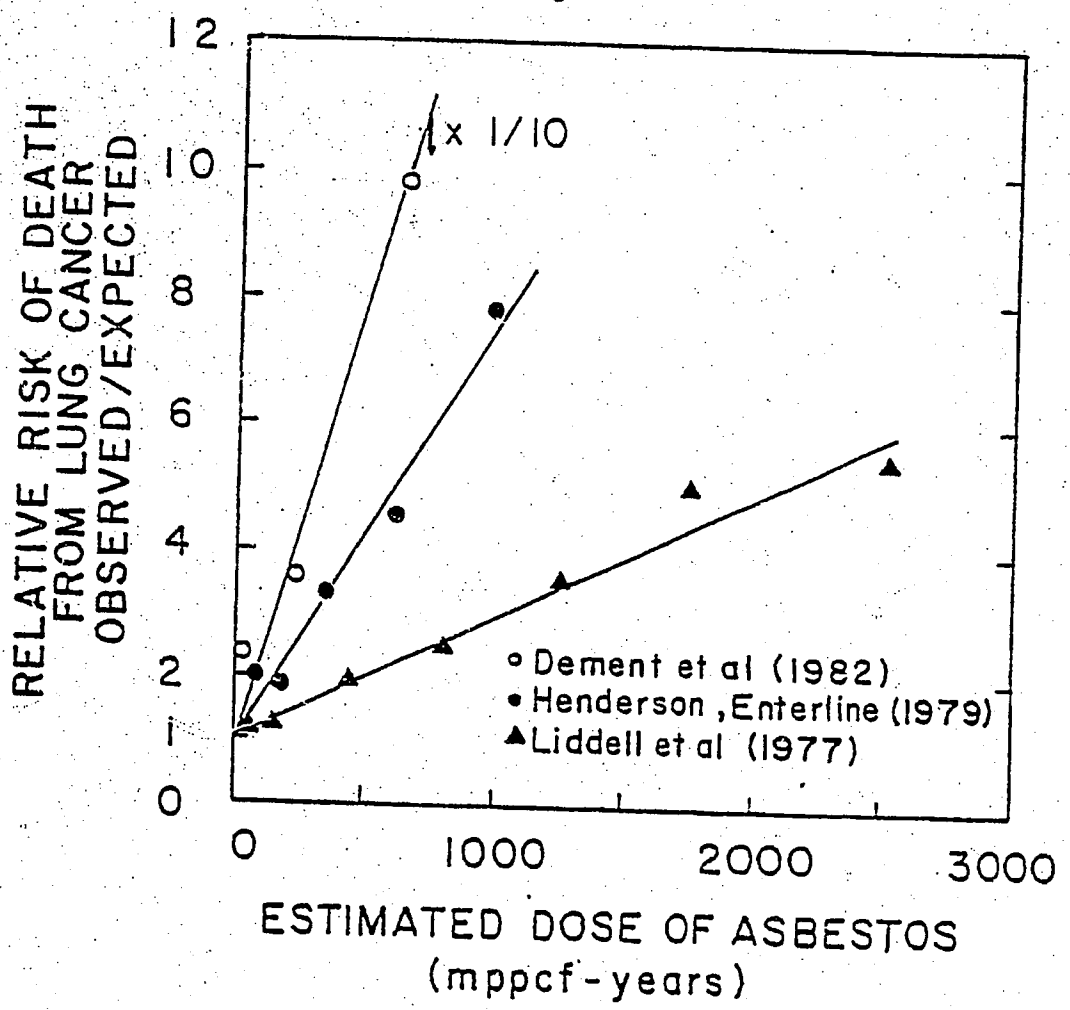

Fig. 3-1 Exposure-response relationship for lung cancer observed in three studies. The cumulative exposures are measured in terms of millions of particles per cubic foot-years (mppcf). Note that the exposure values for the open circles are to be multiplied by 1/10.

ity is plotted against the measured cumulative dust exposure. While different exposure-response relationships appear to exist for the three circumstances, each demonstrates a linear relationship over the entire range of observation. The differences in the slopes of the three relationships may relate to differences in the quantity of the other dust present, the fiber size distribution, the age of the population under observation, and the representativeness of dust sampling program. These factors will be discussed later when the exposure-response relationships of all available studies are compared (Sec. 3.7 Quantitative exposure-response relationships for lung cancer). Further, when exposure-response relationships are analyzed according to duration and intensity of exposure (McDonald et al., 1980), the results are far less dramatic than shown in Figure 3-1. However, this may be the results of small numbers; only 46 excess lung cancer deaths are reported in all exposure categories.

Even fewer data are available on the exposure-response relationship for mesothelioma. Table 3-2 lists the mesothelioma mortality from four studies (Seidman et al. 1979; Hobbs et al. 1980; and Jones et al. 1980) in terms of cases per 1,000 person-years of observation beginning 10 years after first exposure. While few deaths are available for analysis, the data for exposure periods longer than 3 to 5 months are consistent with a linear relationship. There were no deaths from mesothelioma observed in any of the lowest exposure categories, whereas 1 to 2 would have been expected in each study on the basis of a linear dose-response relationship. Similarly, data of Newhouse and Berry (1979) show an increasing risk of mesothelioma with increasing duration and intensity of exposure. However, a quantitative relationship cannot be determined.

This document will use a linear exposure-response relationship for estimating unit exposure risks and for calculating risks at cumulative exposures 10 to 100 times less than those of the occupational circumstances of past years. It is a plausible relationship and no evidence contradicts it, although the strength of the evidence supporting it is limited. It has three distinct advantages: 1) point estimates of ex-

Table 3-2

The risk of death from mesothelioma according to time of asbestos exposure in three studies

Exposure period (months)	Number of deaths	Estimated person years 10+ years from first exposure	Deaths/1000 person years
Hobbs et al. (1980)			
< 3	0	21,213	0
3 - 11	10	19,548	0.5
12+	16	14,833	1.1
Seidman et al. (1979)			
2.2	0	6,640	0
7.1	3	2,000	1.5
15.4	4	2,290	1.7
57	7	2,480	2.8
Jones et al. (1980)			
		# exposed	% of deaths
< 5	0	314	0
5 - 10	3	116	2.6
10 - 20	4	145	2.8
20 - 30	4	101	4.0
30+	5	51	9.8

Newhouse and Berry (1979)

	Duration of exposure	Intensity of exposure: Low-moderate	Intensity of exposure: Severe
Males	< 2 yrs	33	104
	> 2 yrs	93	243
Females	< 2 yrs	{ 48 }	136
	> 2 yrs		360

posure-response can be made without knowledge of individual exposures, i.e., the excess mortality of an entire group can be related to the average exposure of the group, 2) extrapolation to various exposure circumstances can be made easily, and 3) it is likely to be a conservative extrapolation procedure from the point of view of human health. It should be emphasized that linearity of exposure-response obtains only for similar times of exposure and observation among similarly aged individuals with similar personal habits.

3.4 The time and age dependence of lung cancer

A relative risk model has long been assumed to be applicable for the description of the incidence of lung cancer induced by occupational asbestos exposure. Such a model is tacitly assumed in description of mortality in terms of observed and expected deaths. Virtually every study of asbestos workers is described in these terms. Early suggestive evidence supporting it is found in the synergistic action between asbestos exposure and cigarette smoking (Selikoff et al., 1968) in which the lung cancer risk from asbestos exposure depended on the underlying risk in the absence of exposure. Relative risk models have been discussed previously by Enterline (1976), Peto (1976) and Nicholson (1982a) utilized in projections of lung cancer from past asbestos exposure by Nicholson et al. (1982b). Information on lung cancer risk from exposures at different ages is now available from two studies (Selikoff et al. 1979; Seidman et al., 1979). The analyses of these data provide substantial support for the use of such a formulation for lung cancer.

Information from the insulation workers study on the time course of asbestos cancer risk is given in Figure 3-2, which shows the relative risk (here taken to be the ratio of observed-to-expected deaths) of death from lung cancer according to age for individuals first employed between ages 15 and 24 and for those employed between ages 25 and 34. As can be seen, the two curves rise with the same slope and are separated by the ten years of difference in age at first exposure. This suggests that the relative risk of developing asbestos-related lung

Figure 3-2

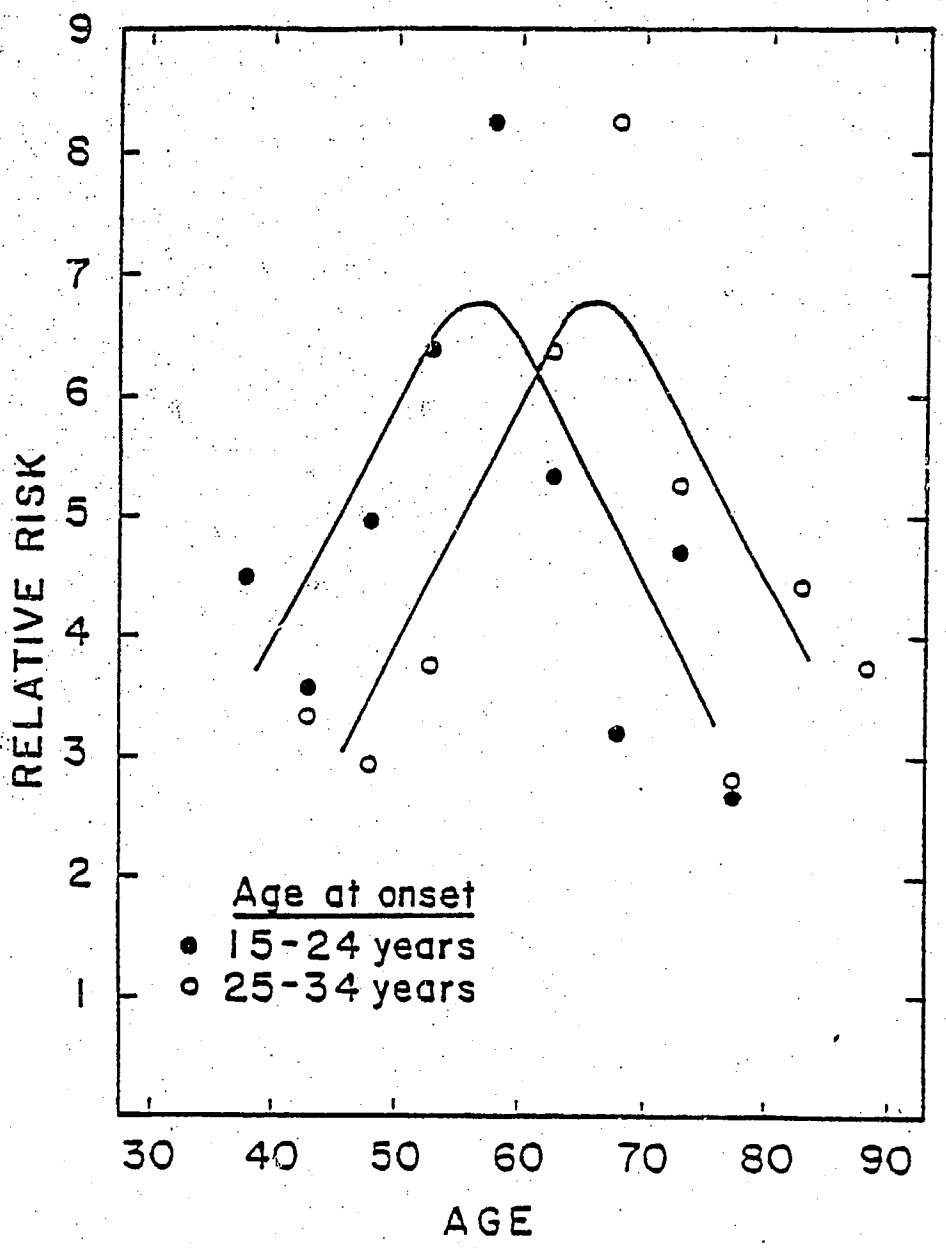

Fig. 3-2 The relative risk of death from lung cancer (observed/ expected) among insulation workmen according to age (• insulators first employed from ages 15-24; o insulators first employed from ages 25-34). Data supplied by: I. J. Selikoff and H. Seidman.

cancer according to time from onset of exposure is independent of age and of the pre-existing risk at the time of exposure. In contrast, both the slope and the value of the excess risk of lung cancer are two to four times greater for the group first exposed at older ages compared to those exposed at younger ages. The similarity of the data for each group in Figure 3-2 suggests that the data be combined and plotted according to time from onset of exposure. The result is shown in Figure 3-3. The data of Figure 3-3 are plotted according to years from onset of exposure. However, because of the great stability of union insulation work, the curve also reflects effects according to duration of exposure up to at least 25 years from onset of exposure. A linear increase with time from onset of exposure is seen for about 35 years (to about the time when many insulators would have terminated employment), after which the relative risk falls substantially. The decrease is, in part, the result of the earlier deaths of smokers from the group under study due to their higher mortality from lung cancer and cardiovascular disease. However, the decrease is not solely the result of the deaths of smokers since a similar rise and fall occurs among those individuals who were smokers at the start of the study compared to smokers in the general population. Part of the decrease may relate to the elimination of asbestos, particularly chrysotile, from the lung; from selection processes, such as differing exposure patterns, (e.g., the survivors may have avoided intense exposures); or from differing individual biological susceptibilities. While the exact reason for the effect is not understood, it is a general phenomenon seen in other mortality studies of asbestons workers (Nicholson, et al. 1979; 1983).

The early portions of the curves of Figures 3-2 and 3-3 have three important features. Firstly, after a short delay, they show a linear increase in the relative risk of asbestos lung cancer according to time from onset of exposure. Secondly, Figure 3-3 shows that this increased relative risk is proportional to the time worked, and, thus, to the cumulative asbestos exposure. However, the linear rise can occur only if the increased relative risk that is created by a given cumulative exposure of asbestos continues to multiply the underlying

Figure 3-3

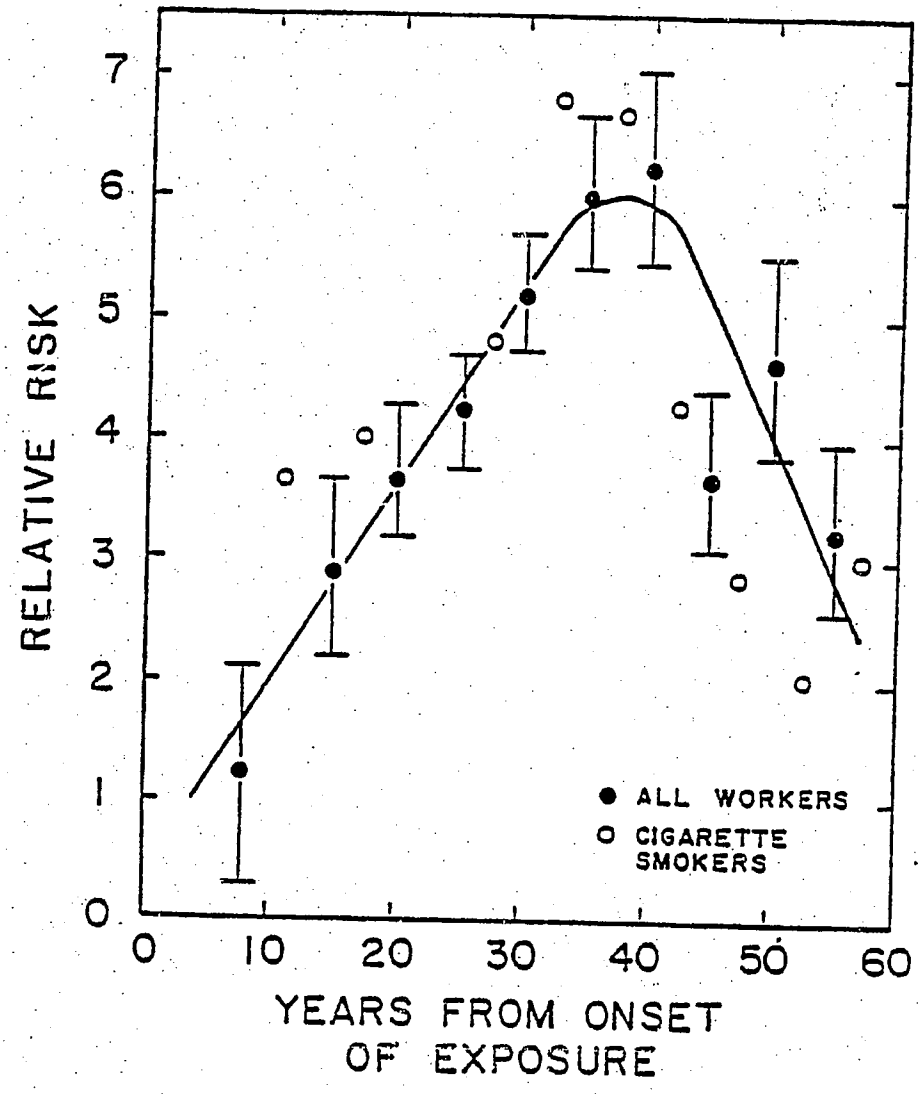

Fig. 3-3 The relative risk of death from lung cancer (observed/expected) among insulation workmen according to time from onset of exposure (● all insulators; o insulators smoking cigarettes at start of follow-up in 1967). Data supplied by: I. J. Selikoff and H. Seidman.

risk for several decades thereafter. Finally, an extrapolated linear line through the observed data points crosses the line of relative risk equal to one (that expected in an unexposed population) at about ten years from onset of exposure. This means that the increased relative risk appropriate to a given exposure is achieved soon after the exposure takes place. However, if there is a low underlying risk at the time of the asbestos exposure (as for individuals aged 20-30), most of the cancers that will arise from any increased risk attributable to asbestos will not occur for many years or even decades until the underlying risk becomes substantially greater.

The data of Seidman et al. (1979) also show that exposure to asbestos multiplies the pre-existing risk of lung cancer and that the multiplied risk becomes manifest in a relatively short time. Figure 3-4 depicts the time course of lung cancer mortality beginning five years after onset of exposure of a group exposed for short periods of time. The average duration of exposure was 1.46 years; 77% of the population was employed for less than two years. Thus, exposure had largely ceased prior to the beginning of the follow-up period. As can be seen, a rise to a significantly elevated relative risk occurred within ten years and then that increased relative risk remained constant throughout the observation period of the study. Furthermore, the relative risk from a specific exposure was independent of the age at which the exposure began, whereas the excess risk would have increased considerably with the age of exposure. Table 3-3 shows the relative risk of death from lung cancer for individuals exposed for less than and greater than nine months is listed according to the age at time of entrance into a ten year observation period. Within a given age category, the relative risk was similar during different decades from onset of exposure, as we saw before in Figure 3-4 with the overall data. However, the relative risk also was independent of the age decade at entry into a ten-year observation period (see lines labeled "All" in each exposure category). There was some reduction in the oldest groups. This may be attributed to the same effects manifest at older ages in insulators and to relatively fewer cigarette smokers who might be present in the older groups because of selective mortality.

Figure 3-4

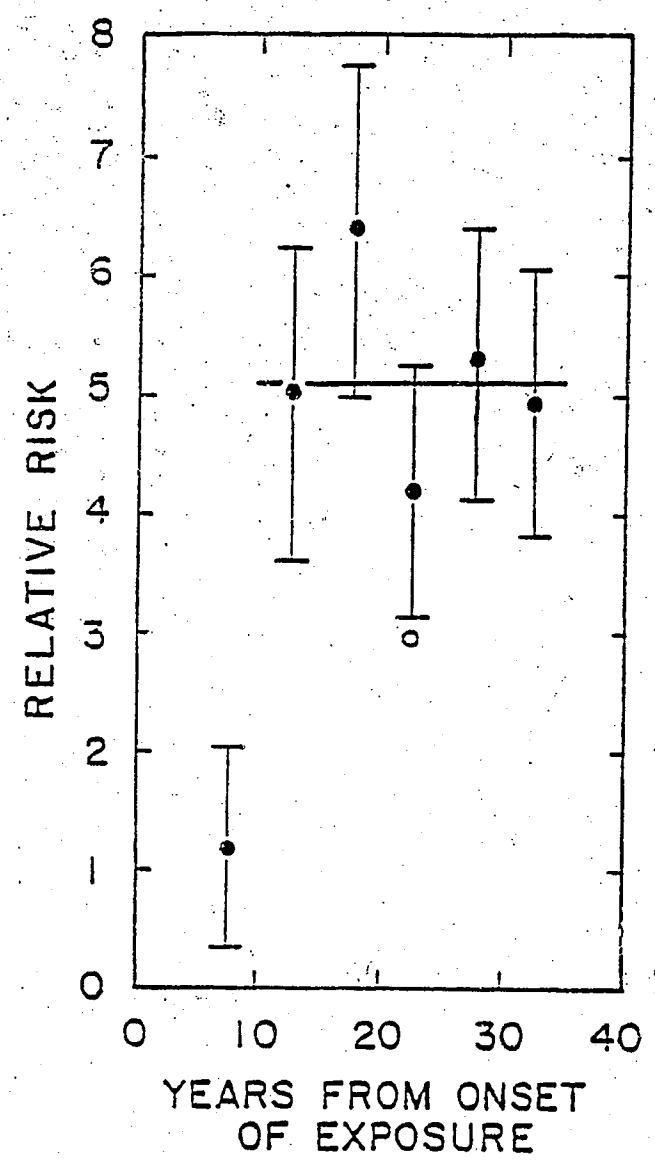

Fig. 3-4 The relative risk of death from lung cancer (observed/ expected) among amosite factory workmen according to time from onset of exposure. From: Seidman et al. (1979)

Table 3-3

Relative risk of lung cancer during ten year intervals at different times from onset of exposure*

Years from onset of exposure	Age at start of period		
	30-39	40-49	50-59
	Lower exposure (<9 months)		
5	0.00 [0.35]	3.75 (2)	0.00 [3.04]
15	6.85 (1)	4.27 (3)	2.91 (4)
25	--	2.73 (2)	4.03 (6)
All	3.71 (1)	3.52 (7)	2.58 (10)
	Higher exposure (>9 months)		
5	0.00 [0.66]	11.94 (4)	9.93 (8)
15	19.07 (2)	11.45 (5)	5.62 (5)
25	--	13.13 (6)	7.41 (8)
All	11.12 (2)	12.32 (16)	7.48 (21)

( ) = Number of cases.

[ ] = No cases seen. Number of cases "expected" on the basis of the average relative risk in the overall exposure category.

* = From Seidman et al. Ann. N.Y. Acad. Sci. 330:61, (1979).

In terms of carcinogenic mechanisms, it would appear that asbestos acts largely like a lung cancer promoting agent. However, because of the continued residence of the fibers in the lung, the promotional effect does not diminish with time after cessation of exposure, as it may with chemical or tobacco promoters. Further, inhalation of the fibers can precede initiating events as the fibers remain continuously available in the lung to act after other necessary carcinogenic processes occur.

A feature of Figure 3-3 that is of importance in the assessment of asbestos carcinogenic risk is the decrease in relative risk after 40 years from onset of exposure or 60 years of age. As mentioned previously, a full understanding of this decrease is not in hand but it has generality. A virtually identical time course of lung cancer risk occurs in asbestos factory employees (Nicholson et al. 1983) and in Canadian chrysotile miners and millers (Nicholson et al. 1979). Because of the significant decrease at long times from onset of exposure and older ages, observations on retiree populations can seriously understate the actual risk of asbestos related death during earlier years. To the extent that time periods between 25 and 40 years from of exposure are omitted from observation, a study will underestimate the full impact of asbestos exposure on death.

To appreciate the effect of the observed lung cancer time dependence upon the results of an epidemiological study, the excess risk of lung cancer was calculated for different observation periods for a hypothetical group exposed for 25 years beginning at age 20. The time course of the risk was set proportional to that of Figure 3-3 and 1978 general population rates were used. Table 3-4 lists the percent excess lung cancer mortality observed for three follow-up periods, 10 years, 20 years, and lifetime, beginning at different ages. As can be seen, the percent excess risk from start of exposure at age 20 to the complete death of all cohort members is 55% of the maximum. The percent excess risk rises up to age 50 as the follow-up period starts later, reflecting the increased relative risk concomitant with increased exposure. For observations starting after age 50, it falls substanti-

Table 3-4

Estimates of the percentage of the maximum expressed excess risk of death from lung cancer for a 25-year exposure to asbestos beginning at age 20[a]

Age at start of observation years	Period of follow-up			Years from onset of exposure
	10 yrs	20 yrs	Lifetime	
20	02	32	55	0
30	34	65	55	10
40	69	91	56	20
50	97	81	55	30
60	73	55	46	40
65	55	41	38	45
70	37	29	29	50

[a] The maximum expressed risk is that manifest 7.5 years after the conclusion of the 25 year exposure.

ally, such that follow-up begun at age 65 observes only 38% of the full risk.

To the extent that a group under observation has an age distribution that is similar to the number alive in each quinqennia in a lifetime follow-up, an observation for any period of time would reflect the same mortality ratio as an observation from onset of exposure to the total death of the cohort. To some extent, this is the case with insulation workers, although they have fewer older individuals than would occur had their mortality been governed by general population data (Their higher risk leads to an earlier death and there is some loss due to lapse in membership). To the extent that the older groups are underepresented, the observed-to-expected risk of 4.60 (BE) as documented by Selikoff et al. (1979) would slightly overestimate the age 20-85+ risk, here calculated to be 4.30 [(7-1)x0.55+1]. Note that the maximum relative risk of insulators is about 7 at 32.5 years from onset of exposure.

The data in Table 3-4 came from observations on long-term exposures to high concentrations of asbestos (>10 f/ml) where preferential death of susceptible individuals occurred. Thus, appropriate comparisons between heavily exposed groups could be made on the basis of lifetime risk (i.e. 55% of the maximum). However, in groups exposed to low levels (<0.1 f/ml), even for many years, selection effects may be much less important. A minimal excess risk would barely affect the pool of susceptibles. A lesser effect would also be expected from short-term exposures (to less than extreme concentrations). For such lower exposures, it would appear that a relative risk unaffected by selection effects would best represent the exposure circumstances. Such risks (at high exposure) are seen in the rising slope of Figure 3-3 and the relative risk seen in Figure 3-4. Other studies will likely be affected by selection effects to some extent.

The above discussion supports a general model for lung cancer in which the excess risk t years from onset of exposure is proportional to the cumulative exposure to asbestos at time t-10 years times the

age and calendar year risk of lung cancer in the absence of exposure. The incidence of lung cancer can be formally expressed by,

$$I_L(a,y,t,d,f) = I_E(a,y)\ [1 - K_L.f.d(t-10)] \qquad \text{(Eq. 1)}.$$

Here, $I_L(a,y,t,d,f)$ is the lung cancer incidence observed or projected in a population of age, a, observed in calendar period, y, at t years from onset of an asbestos exposure of duration, d, and intensity, f. $I_E(a,y)$ is the age and calendar year lung cancer incidence expected in the absence of exposure. If smoking data are available I_L and I_E can be smoking specific incidences. f is the intensity of asbestos exposure in fibers longer than 5 micrometers per ml (f/ml), d is the duration of exposure up to ten years from observation, and K_L is a proportionality constant that is a measure of the carcinogenic potency of the asbestos exposure. A delay in manifestation of risk is based on the data of Seidman et al. (1979) and Selikoff et al (1979); in neither study was any lung cancer seen prior to ten years from onset of exposure. As can be seen from Eq. 1, the relative risk of lung cancer, I_L/I_E, is independent of age and depends only on the cumulative exposure to asbestos.

Different asbestos varieties have different size distributions and the fraction greater than five micrometers depends on fiber type and the production process (Nicholson, et al. 1972; Gibbs and Hwang, 1975). Animal data demonstrate that dimensionality is an important variable in fiber carcinogenicity. Thus, K_L would be expected to depend, to some extent at least, on fiber type and fiber dimension. In practice, however, uncertainties in establishing quantitative dose-response relations, through the application of Eq. 1 to observed data, may preclude the determination of K_L by fiber type.

3.5 Multiple factor interaction with cigarette smoking

The multiplicative interaction between asbestos and the underlying risk of lung cancer is seen in the synergism between cigarette smoking and asbestos exposure which was first identified by Selikoff et al.

(1968). Recent data on U.S. insulation workers confirm and greatly extend the initial findings (Hammond et al. 1979). In this larger study, 12,051 asbestos workers, 20 or more years from onset of their exposure, were followed from 1967 through 1976. At the outset, 6,841 had volunteered a history of cigarette smoking while 1,379 said they had not smoked cigarettes. By January 1, 1977, 299 deaths had occurred among the cigarette smokers, and eight among those without such history.

This experience was compared to an age and calendar year specific basis with that of like men with the same smoking habits in the American Cancer Society's prospective Cancer Prevention Study (Hammond, 1966). 73,763 white males with only a high school education and exposed to dusts, fumes, gases, or chemicals at non-farming work were selected for the control group. The age standardized rates per 100,000 person-years for each group are shown in Table 3-5. The results show that both the smoking and non-smoking lung cancer risk is multiplied five times by the insulator's asbestos exposure. However, since the risk is low for non-smokers, multiplying it five times does not result in many cases, although any excess is clearly undesirable. On the other hand, smoking by itself causes a major increase and when that high risk is then multiplied five times, an immense increase is found. Corroborative data on the multiplicative smoking-asbestos interaction are seen in studies by Berry et al. (1979), McDonald et al. (1980).

The study by Hammond et al. (1979) also carried the asbestos smoking-interaction a step further, to show increased risk of death of asbestosis. As noted previously, insulation work carried a risk of fatal progressive pulmonary fibrosis, and some of those who never smoked cigarettes died of asbestosis. Nevertheless, asbestosis mortality for men who smoked a pack or more a day was 2.8 times higher than that for men who never smoked regularly. Cigarette smoking, with resulting bronchitis and emphysema, adds an undesirable and sometimes unsupportable burden to the asbestos-induced pneumoconiosis. Interactive effects between cigarette smoking and the prevalence of X-ray abnormalities previously have been reported (Weiss, 1971). No rela-

Table 3-5

Age-standarized lung cancer death rates
for cigarette smoking and/or occupational
exposure to asbestos dust compared with
no smoking and no occupational exposure to asbestos dust

Group	Exposure to asbestos?	History cigarette smoking?	Death rate*	Mortality difference	Mortality ratio
Control	No	No	11.3	0.0	1.00
Asbestos workers	Yes	No	58.4	+47.1	5.17
Control	No	Yes	122.6	+111.3	10.85
Asbestos workers	Yes	Yes	601.6	+590.3	53.24

* Rate per 100,000 man-years standarized for age on the distribution of the man-years of all the asbestos workers. Number of lung cancer deaths based on death certificate information.

From Hammond et al (1979)

tionship was found in the Hammond et al. study (Seidman, quoted in Frank, 1979), however, between cigarette smoking and the risk of death from mesothelioma or gastrointestinal cancer.

3.6 Methodological limitations in establishing dose-response relationships

Establishing dose-response relationships for human exposure to asbestos is associated with substantial difficulties. Perhaps the most important is that current health effects are the result of exposures to dust in previous decades, when few and imperfect measurements of fiber concentrations were made. Current estimates of what such concentrations might have been can be inaccurate since individual exposures were highly variable. Further, while disease response now can be established through epidemiological studies, these, too, can be misleading because of methodological limitations. Despite this, useful estimates of risk can be made, to provide an approximate measure of asbestos disease potential in environmental circumstances. Limitations of existing data can be taken into account and their recognition can stimulate appropriate research to fill identified gaps.

The accuracy of exposure-response data for asbestos diseases is limited by our lack of information concerning past fiber exposures of those populations whose mortality or morbidity have been evaluated.. Relatively, few measurements were made in facilities using asbestos fibers prior to 1965. Further, those measurements that were done quantified all dust (both fibers and particles) present in the workplace air. Current techniques, using membrane filters and phase contrast microscopy for the enumeration of fibers longer than five micrometers have been utilized in Great Britain and the United States only since 1964 (Ayer et al., 1965; Holmes, 1965) and have been standardized in the United States only since 1972 (NIOSH, 1972; 1979) and even later in Great Britain.

Modern counting techniques may be utilized to evaluate work practices and ventilation conditions believed to be typical of earlier activi-

ties. However, it is always difficult to duplicate materials and conditions of earlier decades and such retrospective estimates are necessarily uncertain. Alternatively, fiber counting techniques and the particle counting instrumentation of earlier years can be used together to simultaneously evaluate a variety of asbestos-containing aerosols. The comparative readings than serve as a "calibration" of the historic instrument in terms of fiber concentrations. Unfortunately, the calibration depends on the type and size distribution of the asbestos used in the process under evaluation and the quantity of other dust present in the aerosol. Thus, no universal conversion has been found between earlier dust measurements and current fiber counts.

In the United States and Canada those few data that were obtained on asbestos workers' exposures prior to 1965 were based largely upon total dust concentrations measured using a midget impinger. Fibers were inefficiently counted with this instrument because of the use of bright field microscopy. Attempts to compare fiber concentrations with midget impinger particle counts generally showed poor correlations (Ayer et al. 1965; Gibbs and Lachance, 1974) (See Figure 3.5, e.g.). In the United Kingdom, the thermal precipitator was used from 1951 through 1964 in one plant for which environmental data have been published. This instrument, too, does not allow accurate evaluation of fiber concentrations and the variability in the correlation between fiber measurements and thermal precipitator data is reported to be large (Sykes 1977, quoted in Advisory Committee, 1979b) but no specific data were given.

Even with the advances in fiber counting techniques, significant errors may be introduced into attempts to formulate general fiber exposure-response relationships. The convention now in use that only fibers longer than 5 μm be counted was chosen solely for the convenience of optical microscopic evaluation (since surveillance agencies are generally limited to such instrumentation). It does not necessarily correspond to any sharp demarcation of effect for asbestosis, lung cancer, or mesothelioma. While it is readily understood that counting only fibers longer than five micrometers enumerates but a fraction of

Figure 3-5

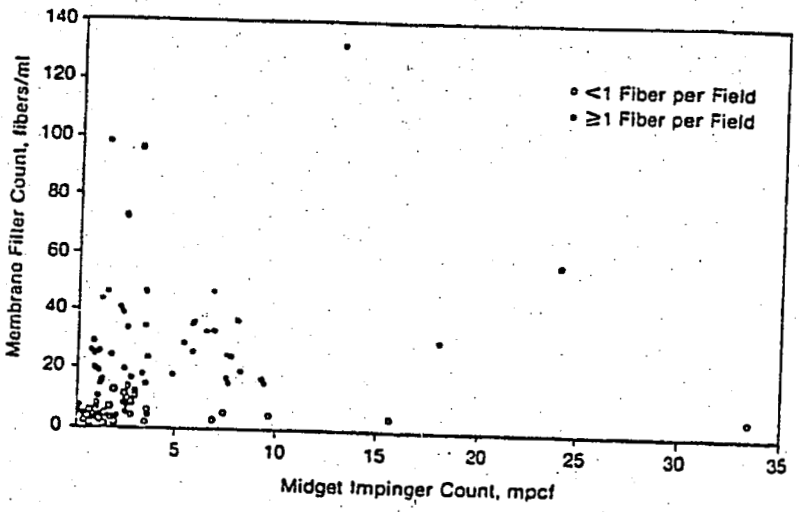

Fig. 3-5 A plot of membrane filter and midget impinger counts; mpcf represents millions of particles per cubic foot. From: Gibbs and LaChance (1974)

the total number of fibers present, there is incomplete awareness that the fraction counted is highly variable. It depends upon the fiber type, the process or products used, and even the past history of the asbestos material (old vs. new insulation material, e.g.), among other factors. For example, the fraction of chrysotile fibers longer than 5 μm in an aerosol can vary by a factor of ten (from as little as 0.5% of the total number to more than 5%). When amosite aerosols are counted, the fraction longer than five micrometers may be 30%, extending the variability of the fraction counted to two orders of magnitude (Nicholson et al. 1972; Nicholson, 1976a; Winer and Cossate, 1979).

Even if consideration is restricted to fibers longer than five microns, many fibers are missed by optical microscopy. Using electron microscopy, Rendall and Skikne (1980) have measured the percentage of fibers with a diameter less than or greater than 0.4 μm (the limit of resolution of an optical microscope) in various asbestos dust samples. In general, they found that more than 50% of the 5 μm or longer fibers were less than 0.4 μm in diameter and, thus, would not be visible using a standard phase contrast optical microscope. Moreover, as with the length distribution, the diameter distribution varied with activity and fiber type. As a result, the fraction of fibers longer than 5 μm visible by light microscopy varied from about 22% in chrysotile and crocidolite mining and amosite/chrysotile insulation manufacture to 53% in amosite mining. Intermediate values of 40% were measured in chrysotile brake lining manufacture and 33% in amosite mill operations. Thus, even perfect measurement of workplace air, with accurate enumeration of fibers according to currently accepted methods, would be expected to lead to different exposure-response relationships for any specific asbestos disease when different work environments are studied. Conversely, risks estimated for a given exposure circumstance must have a large range of uncertainty to allow for the variability resulting from fiber size effects.

Those uncertainties that exist in the physical determinations of past fiber concentrations and our difficulty in evaluating the exposure parameter of importance in current measurements are exacerbated by the

sampling limitations in determining individual or even average exposures of working populations; only few workmen at a worksite are monitored and then only occasionally. Variability in work practices, ventilation controls, use of protective equipment, personal habits and sampling circumstances add considerable uncertainty to our knowledge of exposure.

Variability in exposure-response relationships obtained in different studies can also be attributed statistical variability associated with small numbers and to methodological difficulties in the estimation of disease. Studies can be significantly biased by inclusion of recently employed workers in study cohorts, use of short follow-up periods and improper treatment of the various time factors that are important in defining asbestos cancer. Inadequacies of tracing, particularly, can lead to significant misestimates of disease. Generally from 10% to 30% of an observation cohort will be deceased (sometimes even less). If 10% of the group is untraced and most are deceased, very large errors in the determination of mortality could result, even if no person-years are attributed to the lost-to-follow-up group. Finally, the choice of comparison mortality rates can introduce significant errors. Local rates are generally the most desirable to use, but these may be unstable because of small numbers, or affected by special circumstances (other industry, e.g.). Data on general population worker mortality rates are not available and existing general population rates may overstate the expected total mortality due to a "healthy worker effect" (Fox and Collier, 1976). Proper consideration of smoking habits is important in the determination of lung cancer risks. Unfortunately, full information on the smoking patterns of all individuals in a cohort is often not available.

3.7 Quantitative dose-response relationships for lung cancer

In concept, exposure-response relationships can best be determined from studies in which individal exposures are estimated for each cohort member, subgroups established according to cumulative exposure (with proper consideration of time factors) and an exposure-response

relationship determined from effects observed in all exposure categories. Consistencies in the observed exposure-response relationships strengthen the risk estimates made from such studies. In practice, however, the estimation of individual exposures involves considerable uncertainties. An exposure estimate for each worker must utilize historic data on particle counts and recent measurements of the ratio of fiber to particle concentrations. Unfortunately, complete job histories are not always available for each worker; often only employment departments are known. Secondly, relatively few dust counts were made prior to 1965 and exposure data may not exist for many jobs in a plant. Thirdly, few fiber-particle comparison counts are made and these often demonstrate great variability (See Figure 3-5). Finally, worker mobility may significantly alter his or her exposure from that estimated at a work station. Systematic and random biases that may occur from any of these uncertainties can lead to significant alteration of a measured exposure-response relationship, even in studies demonstrating a near perfect linear relationship.

In some studies, individual exposures are not determined for each cohort member, but only for cancer cases of interest and a selected number of controls. Odds ratios are then calculated according to exposure, but they are limited by the uncertainties of small numbers and confounding effects in addition to all of the uncertainties discussed above.

Finally, two studies will be considered in which information is available only for the group as a whole. Both utilized recent determinations of fiber concentrations in work activities believed to represent those of previous years. While they are not affected by the uncertainties of fiber-particle conversions, they are uncertain because members of each group were exposed to highly variable asbestos concentrations; in one case (insulators), each worker experienced the variable exposure, in the other case (an amosite insulation factory) different workers experienced different exposures but a plant average exposure was estimated. This could be in error to the extent that all jobs were not properly weighted in the sampling program.

In the analysis of eleven studies that follows, all available exposure-response information will be utilized. When such data are inconsistent or possible biases are perceived, alternative analyses will also be undertaken (weighted regression analysis or use of averaged risk-exposure data). A value for K_L will be calculated for each study using either the slope of observed dose response data, the odds ratios of case control analyses or the ratio of excess lung cancer risk to average exposure. These will be listed in Table 3-10 (page 56) and displayed in Figure 3-6 (page 56), along with 95% confidence limits calculated from the expected variance on the observed number of lung cancer cases. For example, consider the study of Peto (1980). In a cohort exposed after 1950, 11 lung cancers were observed and 3.35 expected in the group followed 15 years after first employment. The excess risk is 7.65 cases and K_L = (11 - 3.35)/3.35/250 f-y/ml = 7.65/3.35/250 = 0.0091. Thus the range on K_L will be from K_L (5.4 - 3.35)/7.65 to K_L (19.7 - 3.35)/7.65. The same procedure will also be used in estimating the variability in studies that provide exposure-response data by cumulative exposure category. While the variation in K_L could be calculated from expected variances of the individual exposure categories, the above procedure will yield very similar results. In addition to statistical variations, possible systematic biases considered in the analysis of each study will be displayed in Figure 3-6. Finally, the effect of a ± two-fold range of uncertainty in cumulative exposure will be indicated in Figure 3-6. This two-fold range is a subjective choice, but is felt to be a realistic representation in the uncertainty of all the sampling problems mentioned previously.

3.7.1 Insulation application; United States (chrysotile and amosite)

The previously discussed mortality study of Selikoff et al. (1979) can be combined with information on asbestos exposure for an exposure-risk estimate. The data on insulators' exposure have been reviewed by Nicholson (1976a) and are summarized in Table 3-6. Using the standard membrane filter technique of the U.S. Public Health Service for counting asbestos fibers (NIOSH, 1979), three different laboratories in the United States have found that

the average fiber concentration of asbestos dust in insulation work between 1968 and 1971 ranged from about 3 to 6 f/ml. A similar study in the Devonport Naval Dockyard in Great Britain, with the same techniques, obtained 8.9 f/ml for the average of long-term samples of asbestos concentrations measured during the application of insulation materials aboard ship (Harries, 1971). In the research that led to these data, it was reported that peak exposures could be extremely high. It was not uncommon, for example, for two-to-five minute concentrations of asbestos to exceed 100 f/ml during the mixing of cement. This mixing, however, would only be done perhaps once an hour. Thus, exposures measured during that hour, including the mixing, would seldom average more than 10 f/ml. Similar experiences were subsequently reported by Cooper and Miedema (1973), who stated, "Peak concentrations may be high for brief periods, while time-weighted averages are often deceptively low."

We have direct information on asbestos fiber concentration, measured by the currently prescribed analysis procedures, only since 1966. Insulation materials have changed from earlier years. Fibrous glass has found extensive use, and work with cork is seldom seen today. Moreover, changes in the asbestos composition of insulation products have taken place. Pipe covering and insulation block may have had twice the asbestos content in past years as in 1968-1970. During this period, however, work practices were virtually identical to those of previous years, and during the period of these measurements, few controls of consequence were in use. Thus, dust concentrations measured under these conditions have relevance for the estimate of levels of past years. Considering the possible doubling of asbestos content of insulation materials, the data from the studies listed in Table 3-6 would suggest that the insulators' average exposures in the United States during past years could have ranged from 10 to 15 f/ml for commercial and industrial construction. In marine construction, it may have been between 15 and 20 f/ml. We will use a value of 15 f/ml as an overall average. However, because

Table 3-6

Summary of average asbestos air concentrations during insulation work

Average concentrations of fibers longer than 5 μm evaluated by membrane filter techniques and phase-contrast microscopy

Research group	Average fiber concentration f/ml: Light and heavy construction	Marine work
Nicholson (1975)	6.3	
Balzer & Cooper (1968)		
Cooper & Balzer (1968)	2.7	6.6
Ferris, et al. (1971)		2.9
Harries (1971a, b)		8.9
Average concentrations of all visible fibers counted with a konimeter and bright-field microscopy		
Murphy, et al. (1971)		8.0
Fleischer, et al. (1946)		30-40
Estimates of past exposure based on current membrane-filter data		
Nicholson (1976)	10-15	

From Nicholson (1976)

of the great variability in work activities of this group, the range of uncertainty in the exposure is estimated to be 10 to 45 f/ml and this range is indicated in Figure 3-6.

This information and the data in Figure 3-3 allow one to calculate a lung cancer risk per cumulative unit asbestos exposure (in f-y/ml) from the linearly rising portion of the curve, the slope of which is 0.16 per year or 0.0107 per f-yr/ml (for an exposure intensity of 15 f/ml). However, the data of Figure 3-3 utilized BE in establishing lung cancer mortality. Adjusting to DC diagnosis reduces the value of K_L from 0.0107 to 0.0091 (0.0107 x 3.06/3.60).

3.7.2 Insulation manufacturing; Paterson, N.J. (amosite), Seidman et al. (1979)

The study by Seidman et al. (1979) also can be used for quantitative risk estimates. While no data exist on air concentrations at the time the Paterson factory operated, information, in terms of fiber counts, exists on air concentrations in two other plants that manufactured the same products with the same fiber and machinery. One of these plants, in Tyler, Texas, opened in 1954 and operated until 1971 and the other, in Port Allegany, Pennsylvania, opened in 1964, and closed in 1972. As in the Paterson factory, efforts to control dust in these newer plants were limited. One, in fact, was housed in a low Quonset type building where the confined space exacerbated dust conditions. During 1967, 1970 and 1971, asbestos fiber concentrations in these plants were measured by the U.S. Public Health Service and the results published in the Asbestos Criteria Document of the National Institute for Occupational Safety and Health (NIOSH, 1972). The arithmetic averages of these exposure measurements for Tyler (Plant X) and Port Allegany (Plant Y), obtained using current fiber counting techniques, were, respectively, 39.1 and 28.9 f/ml, with an overall average of 34.9 f/ml. As these two recently operating plants had very similar average exposures, it is unlikely that the Paterson plant would have differed significantly.

The mortality data presented by Seidman et al. (1979) are in a different format from that usually encountered in epidemiological studies. They compared the cumulative mortality, by cause, of a cohort of 820 asbestos exposed men with a similarly aged hypothetical control population followed over the same calendar years. Thus, the number of expected deaths in a time period is based on the number of individuals expected to be alive at the start of the period, rather than on the number alive in the exposed population at the start of the period. Since the mortality of the cohort is considerably above that expected, the number assumed alive at the start of later observation periods is much greater than occurs. Table 3-7 lists the exposure groups of Seidman et al. (1979), the average work period of each group, the estimated cumulative exposure using 35 f/ml as the average intensity of exposure for the group the observed cumulative percentages of deaths (DC) and the expected cumulative percentages of death, adjusted to a person-years-at-risk basis.

A group average cumulative exposure of 51 f-y/ml is calculated from the work duration of all cohort members. This gives a value of 0.068 for K_L [(10.71 obs./2.40 exp. -1)/51 f-y/ml]. The high SMR's at low durations of exposure suggest that general population rates may be inappropriately low for the study group, as all of the short-term exposure categories are proportionately higher than expected (by extrapolating from the longer exposure period data). The underestimate of expected rates may be a factor of 2. This would correspondingly lower K_L in Figure 3-6.

3.7.3 Asbestos products manufacturing; United States (chrysotile and crocidolite), Henderson and Enterline, (1979)

The data of Henderson and Enterline (1979) (Figure 3-1) can also be used to establish fiber dose-response data even though their data were presented in terms of total dust concentrations measured in millions of particles per cubic foot (mppcf). No data exist on the conversion between mppcf and f/ml for most of the

Table 3-7

Observed and expected cumulative probability of death from lung cancer 5 through 35 elapsed years since onset of work in an amosite asbestos factory, 1941-1951 by length of time worked

Length of time worked	No. of men at 5-year point	Average exposure time (years)	Estimated average dose (f-yr/ml)	Expected percentage of deaths[2]	Observed percentage of deaths (DC)		Ratio
< 1 month	61	0.04	1.4	2.95	6.07	(3)[1]	2.06
1 - 2 mo.	90	0.09	3.2	2.70	7.34	(5)	2.72
2 - 3 mo.	82	0.17	5.9	2.79	7.42	(6)	2.66
4 - 6 mo.	148	0.29	10.2	2.47	5.90	(8)	2.38
6 - 12 mo.	125	0.59	20.6	2.15	10.21	(12)	4.74
1 - 2 years	125	1.28	44.8	2.02	12.41	(15)	6.14
2+ years	188	4.77	166.9	2.34	18.51	(34)	7.91
All times	820	1.46	51.1[3]	2.40	10.71	(83)	4.46

1 - ( ) = number of lung cancer deaths
2 - Adjusted to a person-years-at-risk basis
3 - Person weighted average

plants studied. Data do exist on the relationship between fiber and total dust concentrations in textile operations and asbestos cement production. Dement et al. (1982) found a conversion of 3 f/ml/mppcf was appropriate to most textile operations, although Ayer (1965) had earlier suggested a value of 6 f/ml/mppcf. In a plant making asbestos cement pipe and sheets, Hammad et al. (1979) determined the conversion value to be 1.4. It would be expected that the lower value would be most applicable to the Henderson and Enterline circumstance because of the extensive use of cement and other mineral particles in asbestos products manufacturing. The least squares regression line of SMR is SMR = 100 + 0.66 x mppcf. Using a value of 1.5 f/ml/mppcf to represent the conversion relationship, the estimate of K_L is 0.0044 (0.66/100/1.5).

As described previously, observing a cohort beginning at age 65 seriously understates the full impact of asbestos exposure. Most of the workers whose mortality experience was graphed in Figure 3-1 began employment prior to age 25. It was estimated (Table 3-3) that a study of a retiree cohort could understate mortality by as much as 60% relative to the maximum observable risk. A possible 2.5-fold increase in the value of K_L is indicated in Figure 3-6.

3.7.4 Asbestos cement products; United States (chrysotile and crocidolite), Weill et al. (1979) Hughes and Weill (1980)

A study of an asbestos cement production facility also provides exposure-response information (Weill et al. 1979; Hughes and Weill, 1980). However, the data are of limited quality because of uncertainties in the mortality data. While the experience of 5,645 individuals was reported, only 1,791 had been employed for longer than two years. Thus, exposures were limited for most cohort members. However, of even greater significance, tracing was accomplished through information supplied on vital status by the Social Security Administration. This only allowed the vital status of 75% of the group to be determined. Those individuals

untraced were considered alive in the analyses. This can lead to serious misestimates of mortality as, prior to 1970, many deaths, particularly of blacks, were not reported to the Social Security Administration. The percentage of unreported deaths of both sexes ranged from nearly 80% in 1950 to 15% in 1967 (Aziz and Buckler, 1980). Thus, many cohort members could be deceased unbeknownst to the researchers. This is likely to be the source of the extraordinarily low overall reported mortality of the cohort, with deficits of about 40% commonly seen in several exposure categories. (The overall SMR is 68.)

Two methods of adjustment for incomplete trace can be made. In one, the overall SMR for lung cancer is divided by the SMR for causes other than respiratory disease, lung cancer and gastrointestinal cancer. This yields a value of K_L of 0.0060 using a value of 64 mppcf for the group exposure and a fiber-particle conversion factor of 1.4 (Hammad et al., 1979) (1.04 ÷ 0.68)/64/1.4). Alternatively, a regression of SMR on dose yields SMR = 77 + 0.46 x mppcf. The low value of SMR is likely the result of missing deaths. If the percent missing is similar in each category then K_L = 0.043(0.46/100/1.4/0.77). We will use the average of these values, 0.0052, for the point estimate of K_L. The assumption that there is an equal percentage of missing deaths in each category is uncertain. There are more untraced in the lowest category (J. Hughes, personal communication) but a greater percentage of those untraced in the most exposed group may be deceased. If one considers all of the untraced deaths to be in the lowest exposure categories and forces a regression line through the origin, its slope is 0.004, reducing K_L by 44%. This downward adjustment is indicated in Figure 3-6.

3.7.5 Asbestos cement products; Ontario, Canada (chrysotile and crocidolite), Finkelstein (1983)

A recent study by Finkelstein (1983) also relates mortality in an asbestos cement products facility to measured exposures. He

established a cohort of 241 production and maintenance employees from records of an Ontario asbestos cement factory. It consisted of all individuals who had nine or more years of employment beginning prior to 1960. Their mortality experience was followed through October 1980. (An expanded cohort of 751 workers with one or more years of employment has also been reported by Finkelstein (1982), but is not yet published. It yields virtually identical unit risk values.) Impinger particle counts, of varying degress of comprehensiveness were available from various sources (government, insurance company, employer) from 1949 until the 1970's. After 1973, membrane fiber counts were taken. Individual exposure estimates were constructed, based on recent fiber concentrations at a particular job, modified for earlier years by changes in dustiness of that job, as determined by the impinger particle counts. For example, exposure estimates for years 1948-1954 for willow operators, forming machine operators and lathe operators were 40 f/ml, 16 f/ml and 8 f/ml, respectively.

The average cumulative 18 year exposure for the production group in the asbestos cement work was 112.5 f-yr/ml. Seventeen lung cancer deaths were observed versus 2.0 expected from Ontario rates for an SMR of 750. Three deaths versus 2.3 expected occurred in an unexposed group. This yields a value of $K_L = 0.067$ [(8.5-1)/112.5]. Data are also presented on the lung cancer SMR's for separate cumulative exposure categories, but they are so variable because of the few deaths in each exposure category that no exposure-response relationship can be obtained. The first two exposure categories shows risk increasing steeply with exposure, but the last falls significantly, although an extreme mesothelioma and GI cancer risk occurs in it.

We do not know the reasons for the very significant difference in risk seen in two plants (of the same company) producing the same product. The point estimate of risk from Finkelstein et. al. (1983) ($K_L = 0.067$) is thirteen times that of Weill et al. (1979) ($K_L = 0.0052$) even after attempting to correct for the incomplete

trace of the latter study. The exposure estimates of Finkelstein would appear reasonable. In a study of asbestosis in the Ontario plant (Finkelstein, 1982), data comparable to that of Berry, et al. (1979) were obtained. Finkelstein observed prevalence rates of asbestosis of 4% and 6% at 50-99 f-y/ml and 100-149 f-y/ml versus Berry, et al.'s 2.5% and 3.5%. Henderson and Enterline (1979) observed 'SMR's of 231 and 522, respectively, among retirees of cement sheet and shingle work and cement pipe work. These values are more consistent with the higher risk of Finkelstein than the lower one of Weill et al.

3.7.6 Textile products manufacturing; Rochdale, England (chrysotile), Peto, (1980)

The mortality experience from an oft-studied British textile plant (BOHS, 1968; Berry et al. 1979; Knox et al. 1969; Peto, 1980) is difficult to interpret. Firstly, dust concentrations have changed fairly dramatically over the past five decades of plant operations. So, too, have subsequent estimates of those concentrations. No measurements of dust concentrations were made prior to 1951, between 1951 and 1964, thermal precipitators were used to evaluate total dust levels, and thereafter filter techniques similar, but not identical, to those in the United States were used. Average fiber concentrations have been published for earlier years based on a comparison of fiber counting with thermal precipitator techniques (Berry, 1973). Unfortunately, no published data exist on the variability of the correlation between these two techniques, although they are stated to correlate "relatively poorly" (Sykes, 1977 quoted in Advisory Comm., 1979b). Earlier published estimates have been stated to be inaccurate; Berry et al. (1979) reported that a re-evaluation of the work histories indicated that some men had spent more time in less dusty jobs than previously believed and that previous average cumulative doses to 1966 had been overestimated by 50%. Recently, coincident with the finding of considerable asbestos-related disease among recent (post-1951) employees and the British Go-

vernment's review of its asbestos standard, the hygiene officers of the plant have re-evaluated previously reported exposure data. It is now suggested that earlier static sampling methods underestimated personal exposures by a factor of about 2 and that whole field, rather than graticule field, microscopic counting understated fiber concentrations by another factor of 2 to 2.5 (Steel, 1979). Unfortunately, the data on which such revised estimates were made are not provided in the text of the British Advisory Committee Reports, which accepted them (Advisory Comm. 1979a). The comparative fiber concentration estimates are provided by Peto (1980) and listed in Table 3-8. However, again no background data are available.

Evaluation of the new estimates is further clouded by questions concerning the appropriateness of multiplying static sampler concentrations by two. This approach is directly contradicted by published data (See Table 3-9) from the factory on the comparison of static and personal sampling results by job (Smither and Lewinsohn, 1973). Dr. Lewinsohn (personal communication) confirmed these results. He stated that the static sampler concentrations were generally higher than those of the personal samplers of men working at the monitored job. The company placed the static samplers to best reflect the breathing zone dust concentrations of operators while tending machines. Dr. Lewinsohn stated that if the maching were running smoothly, the worker would often leave the site (to talk with fellow workers, go to the rest room, etc.) and experience a lower dust concentration. The difference between static and personal sampling data was greatest in the dustier jobs (compare weaving vs. carding) as men would tend more to leave a dusty area. In the Rochdale factory, the average of the ratios of static to personal sample concentrations at the same work station is 1.8 (1.5 if the fiberizing opertion is not considered). Thus, the fiber estimates published by Peto (1980) reflect what is believed to be an improper adjustment and the range of uncertainty in K_L will reflect this.

Table 3-8

Previous and revised estimates of mean dust levels in fiber/ml (weighted by the number of men at each level) in selected years.

	1936	1941	1946	1951	1956	1961	1966	1971	1974
Previous estimates corresponding to early fiber counts (Peto et al., 1977)	13.3	14.5	13.2	10.8	5.3	5.2	5.4	2.4	-
Revised estimates corresponding to modern counting of static samples*	No measurements prior to 1951			32.4	23.9	12.2	12.7	4.7	1.1

* These estimates are based on preliminary data on 126 men first employed between 1951 and 1955, and should be regarded as provisional.

From Peto (1980)

Table 3-9

Dust levels: Rochdale asbestos textile factory, 1971

Department	Process	Static sampler	Personal sampler
Fiberising	Bag slitting	3	1
	Mechanical bagging	4	1
Carding	Fine cards	3.5	2
	Medium cards	4.5	3.5
	Coarse cards	8	6
	Electrical sliver cards	1.5	1
Spinning	Fine spinning	2.5	3
	Roving frames	6	3
	Intermediate frames	5.5	3
Weaving	Beaming	0.5	0.5
	Pirn weaving	1.5	1
	Cloth weaving	2	1
	Listing weaving	0.5	0.5
Plaiting	Medium plaiting	4	2

From Smither and Lewinsohn, 1973

A second difficulty of the British textile factory study is that the dose-response data calculated from groups exposed before and after 1950 differ considerably. The published fiber concentrations (Peto, 1980) suggest that the pre-1951 group was exposed to about 30 to 40 f/ml prior to 1965 and that of the post-1050 group to about 15-20 f/ml. It is anomalous that more disease is seen in the latter group. An analysis by Peto (1980) suggests the cumulative exposure of the post-1950 group is 250 (200-300) f-y/ml. This dose and mortality data 15 years after onset of exposure yields a value of $K_L = 0.0091$. The corresponding estimate for the pre-1951 group, using 600 f-y/ml for the cumulative exposure is 0.0009. The values for the older group suffer from uncertainties in exposure estimates and that of the younger groups from few deaths in the cohort. Both sets of data suffer from the relatively short time from first exposure of many of the cohort members. As indicated above, uncertainties in exposure estimates could raise these estimates by a factor of 3.

It is difficult to reconcile the differences between the two subcohorts employed in this facility. The data are severely limited by the relatively small size of the cohort and the few deaths available for analysis. Nevertheless, the nearly tenfold difference in the estimated risk of death from lung cancer suggests the possible existence of some unidentified bias in the pre-1951 group. The finding of only a 50% increase in lung cancer in exposure circumstances that led to 5.3% of deaths being from asbestosis is certainly unusual, as is the finding that virtually as many deaths occurred from mesothelioma as lung cancer.

3.7.7 Textile products manufacturing; United States (chrysotile), Dement et al. (1982, 1983a, 1983b)

Mortality data from a chrysotile textile plant studied by Dement et al. (1982, 1983a, 1983b) also allow a direct estimate of lung cancer risk per fiber exposure. Here, data from impinger measurement of total dust in terms of mppcf were available, charac-

terizing dust concentrations since 1930. Further, 1,106 paired and concurrent impinger-membrane filter measurements allowed conversion of earlier dust measurements to fiber concentrations. These showed that 3 f/ml were equivalent to 1 mppcf for all operations except fiber preparation. (The 95% confidence interval was 2 to 3.5 f/ml/mppcf.) A value of 8 f/ml/mppcf characterized fiber preparation work (confidence interval, 5-9). Subsequent to 1940, average fiber concentrations in most operations were estimated to range from 5-10 f/ml with the exception of fiber preparation and waste recovery where mean concentrations were from 10-80 f/ml. A weighted regression line yields SMR = 150 + 4.20 x f-y/ml for a K_L of 0.042.

Dement et al. (1982) used U.S. rates for calculating expected deaths. County rates were 75% higher. Dement et al.'s arguments for the use of national rates are persuasive. (Local rates were probably influenced by nearby shipyard employment and the smoking habits of the study population reflected those of the U.S. general population.) However, a value of K_L reduced by 33% will be indicated. This will bring the SMR at zero exposure to 100 and allow for some consideration of unusually high local rates.

3.7.8 Friction products manufacturing; Great Britain (chrysotile and crocidolite), Berry and Newhouse, (1983)

Newhouse and Berry have analyzed the mortality of a large workforce employed manufacturing friction products. All individuals employed in 1941, or later, were included in the study and the mortality experience through 1979 determined. Exposure estimates were made by reconstructing work and ventilation conditions of earlier years. Fiber measurements from these reconstructed conditions suggested that exposures prior to 1931 exceeded 20 f/ml but those afterwards seldom were in excess of 5 f/ml. From 1970 exposures were less than 1 f/ml. These relatively low intensities of exposure kept the average cumulative exposure for the group to less than 50 f-y/ml.

The overall mortality of all study participants, ten years and more after onset of exposure, was no greater than expected for all causes. Cancer of the lung and pleura was slightly elevated in men (151 obs. vs. 139.5 exp.) but the excess was largely accounted for by eight mesothelioma deaths. No unusual mortality was found in those employed ten or more years. Using a case-control analysis according to cumulative exposure, Newhouse and Berry estimated that the lung cancer increased risk was 0.06% per f-y/ml (K_L = 0.0006) with an upper 90% confidence limit of 0.8% per f-y/ml.

3.7.9 Mining and milling; Quebec, Canada (chrysotile), Liddell et al. (1977); McDonald et al. (1980)

The results reported by Liddell et al. (1977) on mortality according to total dust exposure in Canadian mines and mills can be converted to relationships expressed in terms of fiber exposures. Figure 5-1 indicates a slope of 0.0019/ mppcf-y. Using a value 3 f/ml/ mppcf for the particle fiber conversion factor, K_L = 0.00063. The factor of 3 f/ml/mppcf is the midpoint of the range of 1-5 f/ml/mppcf suggested by McDonald, et al. (1980) as applicable to most jobs in mining and milling.

These studies of the Canadian miners are highly anomalous and indicate a lung cancer risk lower than virtually any other study of asbestos workers. Firstly, the overall risk of lung cancer mortality in all miners is 1.25 times expected. Yet in studies of the mortality of male residents of Thetford, in the midst of the Canadian asbestos mining area (Toft et al., 1981, Wigle, 1977), an excess risk of 1.84 is seen in lung cancer and 2.30 in cancer of the stomach. As no corresponding increases were seen in female cancer rates, Toft et al. (1981) and Wigle (1977) attributed the excesses to occupational exposure in the mines. Siemiatycki (1982) recently showed data from Asbestos and Thetford Mines, Québec that indicated an SMR for lung cancer in males of 148 compared to Québec rates [which may be high by a factor of

1.5 (McDonald et al. 1971) compared to local rates]. Secondly, internal inconsistencies exist in the McDonald, et al. (1980) analysis of the combined effect of asbestos exposure and cigarette smoking. In the lower cumulative asbestos exposure category, the relative risk of death of smokers compared to non-smokers is 11.8, as expected. However, in the medium and high cumulative asbestos exposure categories, the relative mortality risks of smokers to non-smokers are 6.6 and 3.6, respectively. This suggests the possibility of some misclassification of asbestos exposure or of smoking. A final uncertainty of the studies is the large percentage (10%) of untraced cohort members. The bias introduced by such a large proportion of unaccounted-for individuals is unknown. Even how they were treated is not stated.

3.7.10 Mining and milling; Thetford Mines, Canada (chrysotile), Nicholson et al., (1976b, 1979)

Higher risks have been obtained by Nicholson et al. (1976b, 1979) from the mortality experience of a smaller group of miners and millers employed 20 or more years at Thetford Mines, Québec. In the 1979 publication, 178 deaths occurred among 544 men who were employed during 1961 in one of four mining companies. In the ensuing 16 years of follow-up, 26 deaths occurred from asbestosis and 28 (25 on DC) from lung cancer (11.1 expected), and one from mesothelioma.

In this study, fiber measurements were made during 1974 in five mines and mills, and data on particle counts were supplied by the Canadian Government. From these data, exposure estimates were made for each of the 544 individuals according to their job history. Fiber exposures for earlier years were estimated by adjusting current measurements by changes in particle counts observed since 1950.

The mortality experience of the whole group has been reported by two exposure categories (Nicholson, 1976b). The first of the two

exposure categories corresponded to a 20 year cumulative dust exposure of 560 f-y/ml. The lung cancer SMR in this group was 1.55 (7 observed, 4.52 expected). In the second category, with a cumulative exposure of 1,760 f-y/ml, the SMR was 4.33 (13 observed, 3.00 expected). The difference between these two values suggests that K_L = .0023 (3.33-0.55)/ (1760-560). However, Québec rates were used to estimate expected deaths and these may overestimate mortality. McDonald et al. (1971) have stated that the local rates of five contiguous counties are two-thirds those of the Province. Thus, K_L should be increased by a factor of 1.5 to 0.0034, or 0.0030 on the basis of DC lung cancer diagnosis. Such an adjustment also makes a straight line through the two SMR's pass close to the value of 100. The effect not adjusting K_L is indicated in Figure 3-6.

3.7.11 Mining and milling; Italy (chrysotile), Rubino et al. (1979)

A final study of chrysotile mining and milling is that of Rubino, et al. (1979) of the Balangero Mine and Mill, northwest of Turin. A cohort was established of 952 workers, each with at least 30 calendar days of employment between January 1, 1930 and December 31, 1965, who were alive on January 1, 1946. Ninety-eight percent of the cohort was traced and their mortality experience through 1975 was ascertained. Overall, an exceptionally high mortality was seen compared to that expected; 332 deaths were observed versus 214.4 expected. The excess mortality, however, was largely confined to non-malignant respiratory disease, cardiovascular diseases, and accidents. The overall SMR for all malignant neoplasms was 106, with only cancer of the larynx found to be significantly in excess in the whole group. While the overall data were relatively unremarkable, the age standardized rates of lung cancer according to cumulative dust exposure showed a relative risk of 2.54 for a high exposure group (376 f-y/ml) compared to a low exposure group (75 f-y/ml) [K_L=0/0051=1.54/ 376-75)]. A case-control analysis of the lung cancer according to cumulative dust exposure showed a relative risk of 2.89.

Thus, K_L lies between 0.005 and 0.006 from the analyses according to dust exposure. However, the relatively low overall risk for lung cancer in the entire group (11 cases observed and 10.4 expected) suggests that the excess risk could be zero.

The results of all the determinations of K_L, the fractional increases in lung cancer risk per f-y/ml exposure, are displayed in Figure 3-6, along with estimates of statistical variation, adjustments for possible biases, and estimates of uncertainties associated with exposure determinations. The details of the calculations of statistical uncertainty are provided in Table 3-10. As can be seen, the range of individual values of K_L is large. Many of the differences may be the result of statistical variation associated with small numbers. Several studies have 95% statistical confidence limits exceeding an orders of magnitude. While the study of insulators could have the widest uncertainty in exposure estimates, its low statistical variance gives it considerable strength. Considering the statistical variability and other uncertainties in the data, the agreement is fairly good. The ranges of all but one estimate of K_L lie between 0.005 to 0.03. The only estimate of K_L that lies outside this range is that made from the study of Liddell et al. (1979). There is no evidence in this analysis that would suggest that a special carcinogenic potency is ascribable to an individual type of fibers. Some of the highest and lowest value for K_L are obtained from pure chrysotile exposures. Exposures involving a mixture of fibers, including amosite and crocidolite, also span a large range of values for K_L. Wide differences also occur in the results of separate epidemiological studies of nearly identical work conditions. This would suggest a midpoint estimate for K_L of about 0.01, but with an uncertainty of about three-fold.

3.8 The Time and Age Dependence of Mesothelioma

In contrast to lung cancer, for which a relative risk model well explained the data, mesothelioma is best described by an absolute risk model, in which the incidence is independent of the age at first exposure and increases according to a power of time from onset of exposure. The rationale for such a model describing human carcinoge-

Figure 3-6

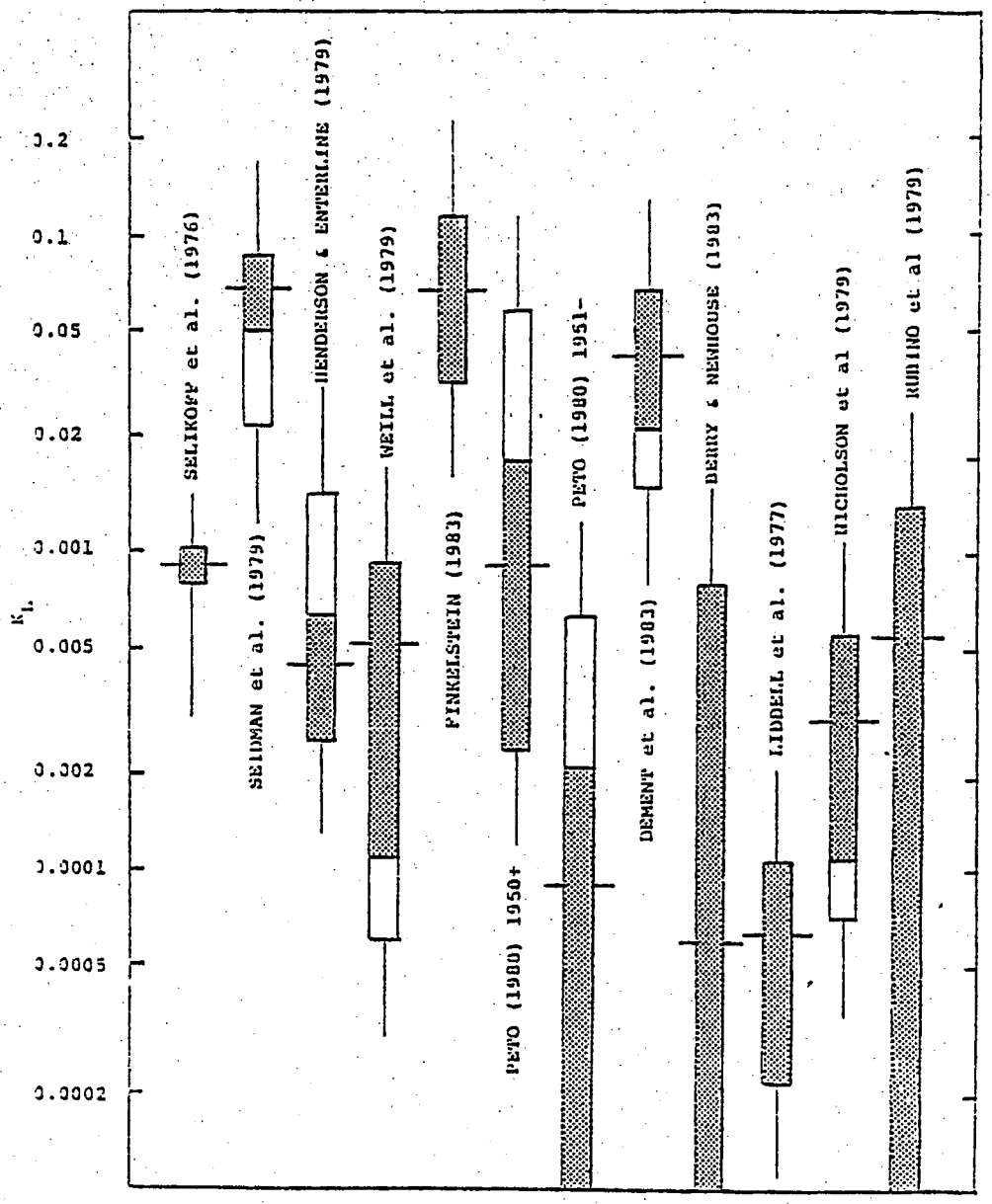

Fig. 3-6 The values for K_L, the fractional increase in lung cancer per f-y/ml exposure in eleven asbestos exposed cohorts. The shaded bar is the 95% confidence limits on K_L associated with the statistical variability of number of cases observed. The open bar is adjustments associated with possible biases. The line is estimated uncertainties associated with exposure estimates.

Table 3-10

Computational data on the statistical variability associated with K_L

	K_L	expected	observed	excess	range on observed	range on K_L
Selikoff, et.al.	0.0091	105.6	429	324.4	388.4 - 469.6	0.0079 - 0.010
Seidman, et.al.	0.068	18.5	83	64.5	65.1 - 100.9	0.0049 - 0.0087
Henderson and Enterline	0.0044	23.3	62	39.7	46.6 - 77.4	0.0026 - 0.0060
Weill, et.al.	0.0051	(32.2)[a]	51	(17.8)[a]	37.0 - 65.0	0.0014 - 0.0094
Finkelstein	0.067	2.0	17	15.0	9.9 - 27.2	0.035 - 0.110
Peto, et.al. (> 1950)	0.0091	3.35	11	7.65	5.4 - 19.7	0.0024 - 0.019
Peto, et.al. (< 1950)	0.0009	16.83	26	9.17	17.0 - 38.0	0.00002- 0.0021
Dement, et.al.	0.042	9.8	33	23.2	22.7 - 46.3	0.023 - 0.066
Berry and Newhouse	0.0006	Case-control calculations				
Lidell, et.al.	0.0006	184	230	46	200.3 - 259.7	0.0002 - 0.001
Nicholson, et.al.	0.0030	7.5	20	13.9	12.2 - 30.8	0.0010 - 0.0083
Rubino, et.al.	0.0055	Case-control calculations				

[a] adjusted for low trace

Case 01-01139-AMC Doc 17702-4 Filed 12/22/07 Page 63 of 75

nesis has been discussed by several authors (Armitage and Doll, 1960; Pike, 1966; Cook et al., 1969, e.g.). Such a model was utilized by Newhouse and Berry (1976) in predicting mesothelioma mortality among a cohort of factory workers in England. Specifically, they matched the incidence of mesothelioma to relationship, $I_M = c(t - d)^k$ where I_M is the mesothelioma incidence at a time t from onset of exposure, d is a delay in the expression of the risk, and k are empirically derived constants. Additionally, the incidence of asbestos-induced mesothelioma in rats (Berry and Wagner, 1969) followed this time course. In the case of the analysis of Newhouse and Berry, the data suggested that the value of k was between 1.4 and 2 and w between 9-11 years. However, the relatively small number of cases available for analysis led to a large uncertainty in the values estimated for either k or d. Peto et al (1982) have recently analyzed mesothelioma incidence in five groups of asbestos-exposed workers. In one study analyzed, that of Selikoff et al. (1979), the number of cases of mesothelioma were sufficiently large that the age dependence of the mesothelioma risk could be investigated. Peto et al. (1982) showed that the absolute incidence of mesothelioma was independent of the age at first exposure and that a function, $I_M = ct^{3.2}$, fit the data well between 20 and 45 years from onset of exposure. However, observed incidence rates for earlier times were leas than those projected, and the authors suggested that an expression proportional to $(t - 10)^2$ better fit the data up to 45 years from onset of exposure. The analysis of Peto et al. (1982) was largely confined to individuals first employed between the years 1922 and 1946; the fit to the mortality of the entire group (including those exposed before and after that span) suggests a value of k greater than 3.2.

Figure 3-7 shows the risk of death of mesothelioma according to age for individuals exposed first between ages 15 and 24 and between ages 25 and 34 as in Figure 1. As can be seen, these data, although somewhat uncertain because of small numbers, roughly parallel one another by 10 years as did the increased RR for lung cancers. Thus, the absolute risk of death from mesothelioma appears to be directly related to onset of exposure and is independent of the age at which the exposure occurs. The risk of death from mesothelioma among the insulation

Figure 3-7

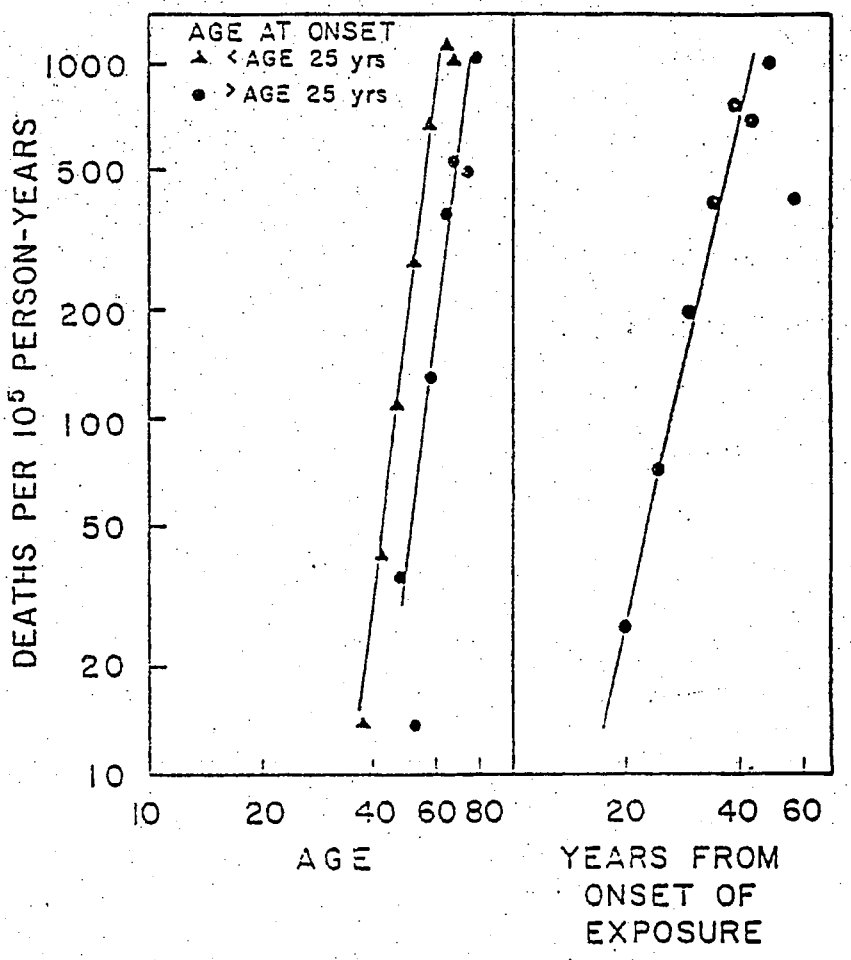

Fig. 3-7 The risk of death from mesothelioma among insulation workmen according to age and years from onset of exposure. The risk of death according to age is shown separately for insulators first employed before age 25 and after age 25. Data supplied by: I. J. Selikoff and H. Seidman

workers is plotted according to time from onset of exposure on the right side of Figure 3-7. It increases about 45 or 50 years from onset of exposure and then appears to fall. Whether the decrease is real or simply the result of misdiagnosis of the disease in individuals age 70 and older or the result of statistical fluctuations associated with small numbers is not certain.

Mesothelioma risk from a short-term exposure can be considered to increase at $c(t - 10)^k$, where k is between 2 and 4 and c is proportional to the short-term cumulative exposure. Using a value of R = 3 (which best fits the insulators data), this leads to the following relations for varying times of exposure:

$$I_M(t,d,f) = K_M\, f[(t-10)^3 - (t-10-d)^3] \qquad t > 10+d \qquad \text{(Eq. 2a)}$$

$$= K_M\, f(t-10)^3 \qquad 10+d > t > 10 \qquad \text{(Eq. 2b)}$$

$$= 0 \qquad 10 > t \qquad \text{(Eq. 2c)}$$

Here I_M is the mesothelioma incidence at t years from onset of exposure to asbestos for duration d at a concentration f. K_M is carcinogenic potency and may depend on fiber type and dimensionality. Note that I_M depends only upon exposure variables and not upon age or calendar year period.

The use of a model for mesothelioma with a delay period versus one that rises at t^k has some distinct advantages. Firstly, it fits the full time course of insulator data better. Secondly, after 45 years from onset it rises less rapidly than a function with no delay. The evidence from two studies (Selikoff et al., 1979 - See Figure 3-7; Nicholson et al., 1983) is that mesothelioma risk after 45 years from onset of exposure ceases to rise and perhaps falls. Thus, a function with a ten year delay is less likely than one without to overstate the lifetime risk of mesothelioma in individuals exposed early in life.

3.9 Quantitative dose-response relationships for mesothelioma

Four of the above studies provide information on the incidence of mesothelioma (pleural and peritoneal combined) according to time from

onset of exposure and data that would allow estimates to be made of the duration and intensity of asbestos exposure. Thus, values for K_M, the potency factor for mesothelioma risk in Eqs. 2a-2c can be estimated. Other studies have reported cases of mesothelioma, but incidence data are lacking. In some of these other studies, the incidence data simply not provided. In others, it was not given because very few mesothelioma deaths were seen. Thus, some studies with missing data could be those in which a lower value of K_M obtains. It should be recognized that we are estimating values of K_M from a biased sample of those studies in which K_L was estimated. A measure of the bias can be estimated by a comparison of the values of K_M and K_L obtained in each analysis. The estimate of K_M for each of the four studies was made by calculating a relative mesothelioma incidence using Eq. 2 and data on duration and intensity of asbestos exposure. The relative incidence curves were then superimposed on the observed incidence data in each study. These fits are depicted on Figures 3-8 and 3-9. The four studies are described below and summary data listed in Table 3-11.

3.9.1 Insulation application; Selikoff et al. 1979; Peto et al. 1982

A follow-up through 1979 of the cohort of insulators provides data on the incidence of mesothelioma with time from onset of exposure (Peto et al. 1982). It has been estimaged that their time-weighted average exposure was 15 f/ml (Nicholson et al. 1976a). Using these data and 25 years for their average duration of exposure, a value of $K_M = 1.5 \times 10^{-8}$ is estimated.

3.9.2 Amosite insulation manufacturing; Seidman et al. 1979

The average employment time of all individuals in this factory was 1.46 years. This value and the previously used value of 35 f/ml for the average exposure yields an estimate for K_M of 5.7×10^{-8}.

Figure 3-8

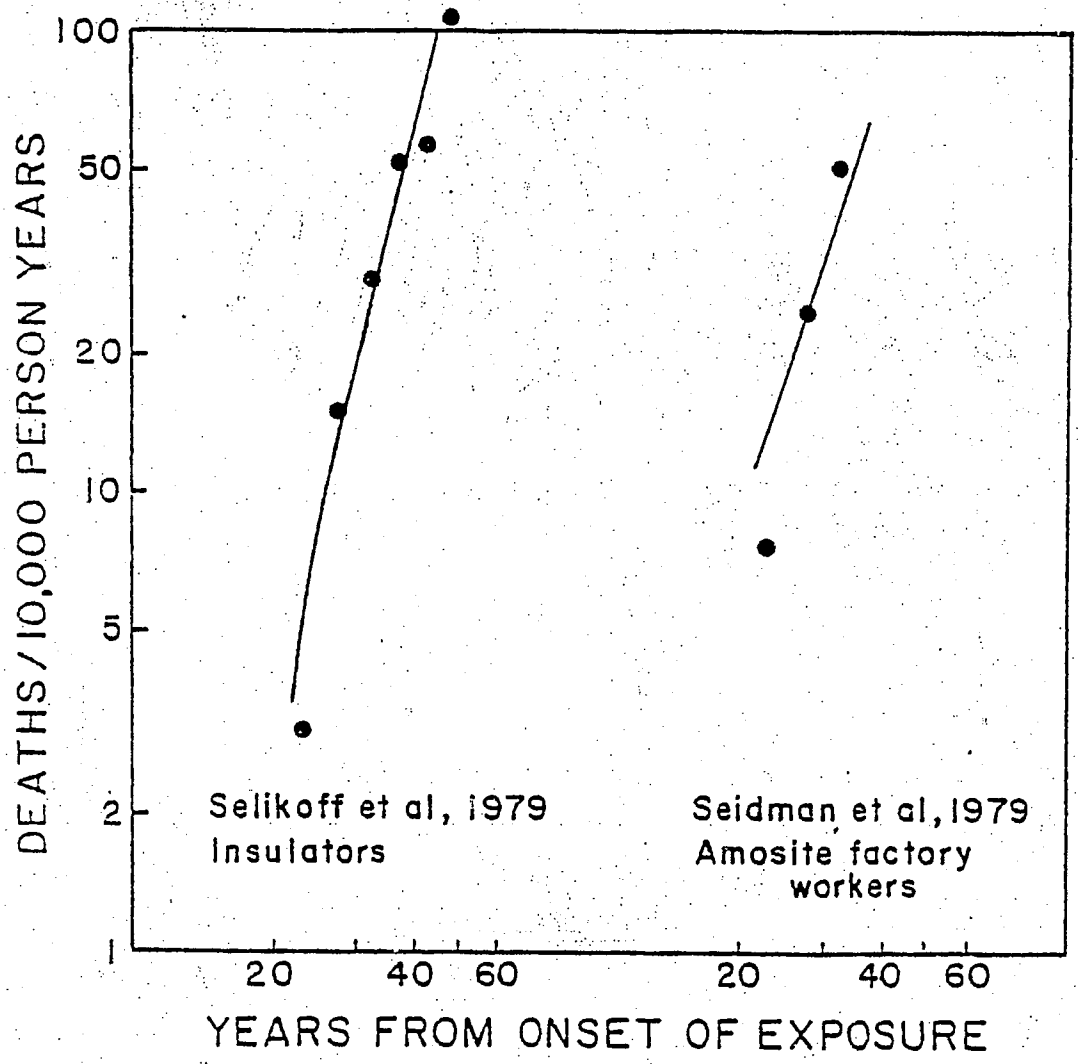

Fig. 3-8 The match of curves calculated using Equation 2 to data on the incidence of mesothelioma in two studies. The fit is achieved for $K_M = 1.5 \times 10^{-8}$ for insulators data and $K_M = 5.7 \times 10^{-8}$ for the amosite workers data. Data from: Peto et al., 1980; Selikoff et al., 1979; Seidman et al., 1979.

Figure 3-9

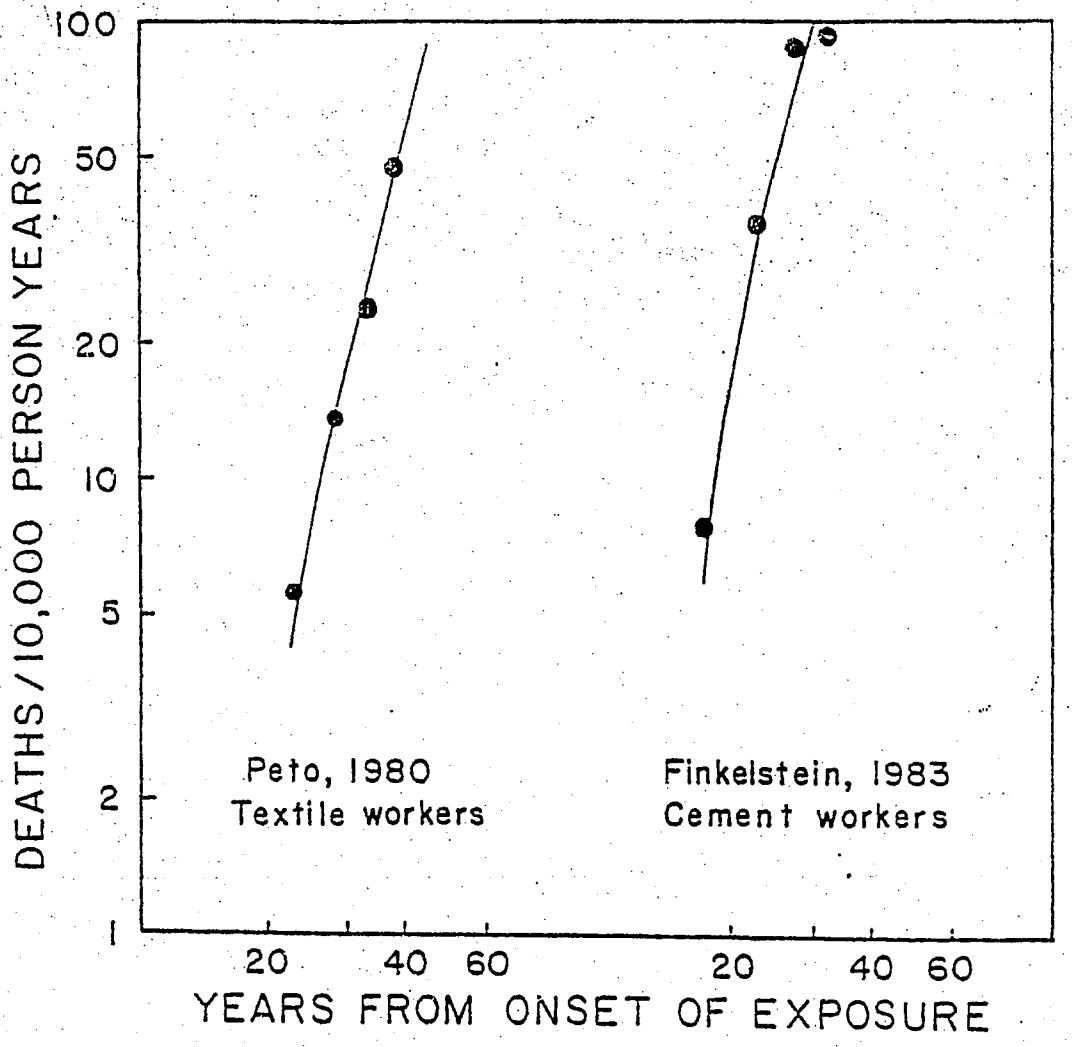

Fig. 3-9 The match of curves calculated using Equation 2 to data on the incidence of mesothelioma in two studies. The fit is achieved for $K_M = 0.7 \times 10^{-8}$ for the textile workers data and $K_M = 1.2 \times 10^{-7}$ for the cement workers data. Data from: Peto et al., 1980; Finkelstein. 1983.

Table 3-11

Summary of the data on K_M, the measure of mesothelioma risk per fiber exposure in four studies of asbestos workers

Study	Average employment duration	Average exposure (f/ml)	K_M	K_M/K_L
Insulators (Selikoff, et al, 1979; Peto et al, 1982)	25	15	1.5×10^{-8}	1.6×10^{-6}
Textile workers (Peto, 1980; Peto et al, 1982)	25	30	0.7×10^{-8}	0.3×10^{-6}
Amosite factory workers (Seidman et al, 1979)	1.5	35	5.7×10^{-8}	0.8×10^{-6}
Cement factory workers (Finkelstein et al, 1983)	12	9	1.2×10^{-7}	1.7×10^{-6}

3.9.3 Textile products manufacturing; Peto, 1980; Peto et al. 1982

A value of 30 f/ml is suggested by the data presented by Peto (1980). However, some uncertainty exists concerning this value as discrepancies in the relative exposures measured using personal samplers and static samplers exist (see above). If the exposures measured by personal samplers are less than static samplers, as suggested by the data of Smither and Lewinsohn (1973), the average exposure could be about 15 f/ml. Using 30 f/ml and an employment period of 25 years a value of $K_M = 0.7 \times 10^{-8}$ is estimated.

3.9.4 Asbestos cement products; Ontario, Canada, Finkelstein, 1983

The cumulative exposure of the cohort over 18 years was 112 f/yr. Only men with nine or more years of employment were included in the cohort. While data on the exact duration and intensity of exposure are unavailable, we will use a value of 12 years for duration of exposure and 9 f/ml for the intensity of exposure. This yields a value of $K_M = 1.2 \times 10^{-7}$.

These are plotted in Table 3-11 and show remarkable consistency between the ratio of K_M/K_L. The four studies suggest that a ratio of K_M/K_L of 10^{-6} is appropriate and that a range of from 3×10^{-9} tp 3×10^{-8} for K_M would appropriately represent most exposure situations.

3.10 Asbestos Cancers at Extra-Thoracic Sites

The consistency of an increased cancer risk and its magnitude, either in absolute (observed-expected deaths) or relative (observed/expected deaths) terms is less for cancer at other sites. Nevertheless, many studies document significant cancer risks at various gastrointestinal (GI) sites. Cancer of the kidney has also been found to be significantly elevated in two large studies (Selikoff et al., 1979; Puntoni et al., 1979). Among female workers, ovarian cancer has been found in excess (Newhouse et al (1972). While no other specific sites have

been shown to be elevated at the 0.05 level of significance, the category of all cancers other than the lung, GI tract or mesothelioma is significantly elevated (Selikoff et al., 1979, e.g.)

Table 3-12 lists all studies in which more than 10 GI cancers were expected or observed and in which the overall lung cancer risk was elevated at the 0.05 level of significance. This choice eliminated many smaller studies, with statistically uncertain data, from consideration, as well as several large studies that demonstrated a low risk of lung cancer, either because of exposure or follow-up circumstances. As the excess risk of GI cancer is less than that of the lung, significantly elevated risks are unlikely to be seen in studies that demonstrate little lung cancer risk. Negative data in such studies do not carry great significance. In considering Table 3-12, it is noteworthy that all but one of the listed studies show an excess GI cancer risk, albeit in three studies, the risk is small. Five of the 13 studies, however, demonstrate the risk at an 0.05 level of significance. Figure 3-10 displays the relationship between the relative risk of lung cancer and relative risk of GI cancer in the 12 studies with excess GI cancer risk. As can be seen, there is a consistent relationship between a greater GI cancer risk and and increased lung cancer risk. Fiber exposure to the GI tract is clear as the majority of fibers inhaled are brought up from the respiratory tract and swallowed (Morgan et al., 1975). Additionally, some may become entrapped within the gut wall (Storeygard and Brown, 1977). Nevertheless, the magnitude of the excess at GI sites is much less than for the lung. In recent studies, the GI excess is about 10-15% of the lung excess.

Table 3-12 also lists the observed and expected mortality for cancers other than mesothelioma and the GI or respiratory tract. The elevation is not as consistent as for GI cancer. Only three studies have elevated risks that are significant at 0.05 level and deficits are observed in three. The analysis is further complicated by the possibility that misattribution of lung cancer or mesothelioma may have occurred for some cases. For example, brain or liver cancers could be

Figure 3-10

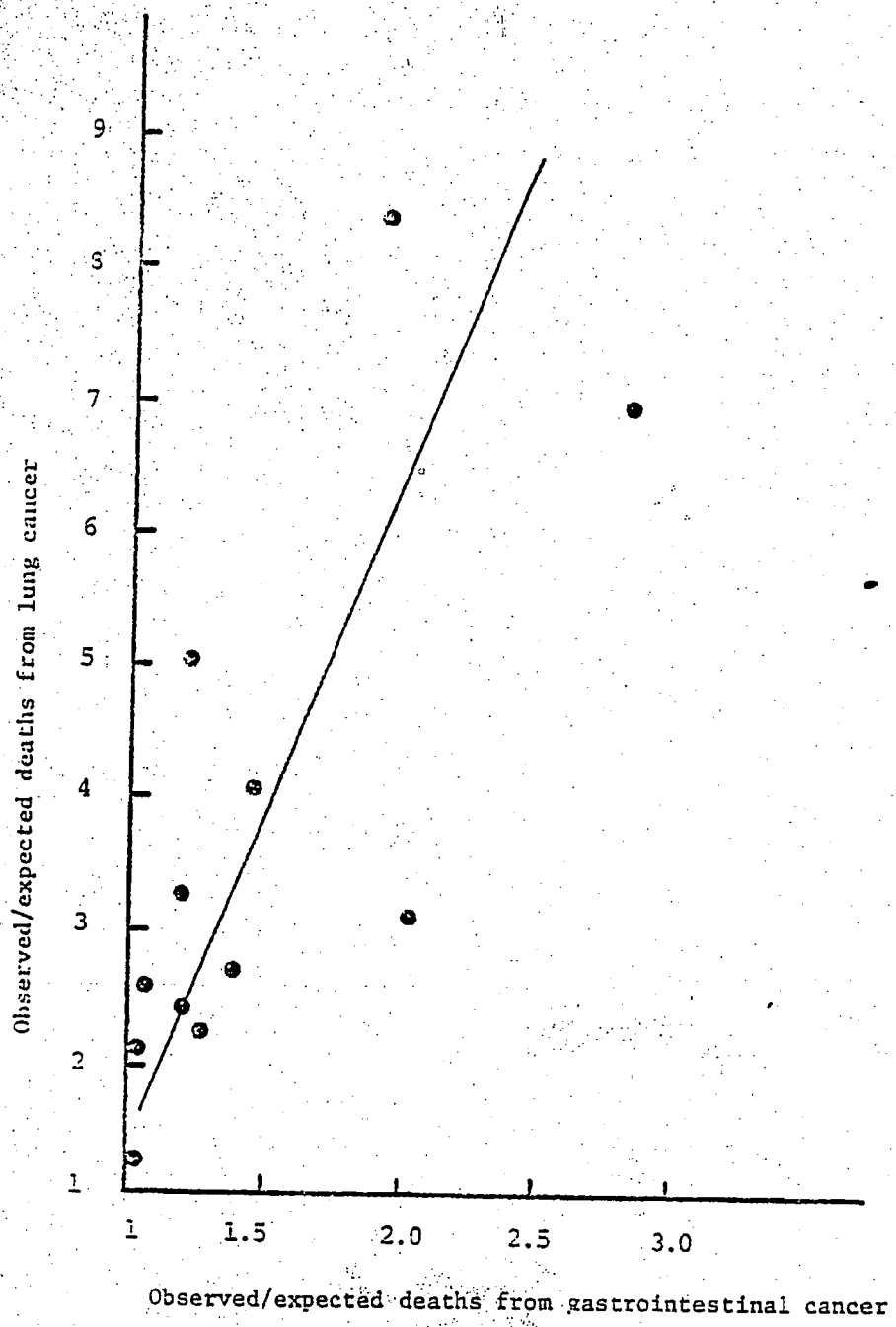

Fig. 3-10 The ratio of observed to expected mortality from lung cancer versus the ratio observed to expected mortality from gastrointestinal cancer.

Table 3-12

Observed and expected deaths for various causes in selected mortality studies

	Respiratory cancer 162-164			Digestive cancer 150-159				Other cancers ex 150-59,162-4, meso			
	O	E	O-E	O	E	O-E	$\frac{(O-E)_d}{(O-E)_r}$	O	E	O-E	$\frac{(O-E)_o}{(O-E)_r}$
Henderson and Enterline (1979)	63	23.3	39.7	55	39.9	15.1	0.380	55	45.6	9.4	0.237
McDonald et al. (1980)	230	184.0	46.0	276	272.4	3.6	0.078	237	217.4	19.6	0.426
Newhouse and Berry (1979) (male)	103	43.2	59.8	40	34.0	6.0	0.100	38	27.4	10.6	0.177
Newhouse and Berry (1979) (female)	27	3.2	23.8	20	10.2	9.8	0.412	33	20.4	12.6	0.529
Selikoff et al. (1979) (NY-NJ)	93	13.3	79.7	43	15.0	28.0	0.351	28	24.5	3.5	0.044
Selikoff et al. (1979) (US)	429	105.6	381.4	122	84.1	37.9	0.099	184	131.8	52.2	0.137
Nicholson et al. (1979)	28	11.0	17.0	10	9.5	0.5	0.029	10	16.1	(6.1)	0.358
Peto et al. (1977)	51	23.8	17.2	16	15.7	0.3	0.019	18	24.8	(6.8)	0.395
Mancuso and El-Attar (1967)	30	9.8	20.2	15	7.1	7.9	0.527	20	6.8	13.2	0.653
Puntoni et al. (1979)	123	54.9	68.1	94	76.6	17.4	0.255	88	81.3	6.7	0.098
Seidman et al. (1979)	83	21.9	61.1	28	22.7	5.3	0.087	39	35.9	3.1	0.037
Jones et al (1980)	12	3.8	8.2	10	20.3	(10.3)	def.	35	39.5	(4.5)	def.
Dement et al (1983b)	33	9.8	23.2	10	8.1	1.9	0.082	11	14.1	(3.1)	def.

Case 01-01139-AMC Doc 17702-4 Filed 12/22/07 Page 74 of 75

metastatic lung cancers in which the primary was not properly identified. In the study of insulators, Selikoff et al. (1979) found that 26 of 49 pancreatic cancers were misclassified; most of the misclassified were peritoneal mesotheliomas. As with GI cancer, the excess at other sites is much less than lung cancer and generally less than GI cancer.

3.11 Asbestosis

The long-term disease entity, asbestosis, resulting from the inhalation of asbestos fibers is a chronic, progressive pneumoconiosis. It is characterized by fibrosis of the lung parenchyma, usually radiologically evident only after ten years from first exposure, although changes can occur earlier following more severe exposures. Shortness of breath is the primary symptom; cough is less common; and signs such as rales, finger clubbing, and, in later stages of the disease, weight loss appear in a proportion of cases. The disease was first reported eight decades ago (Murray, 1907) and has occurred frequently among workers occupationally exposed to the fiber in ensuing years. Characteristic X-ray changes are small, irregular opacities, usually in the lower and middle lung fields, often accompanied by evidence of pleural fibrosis or thickening, and/or pleural calcification. Both the visceral and, more commonly, parietal pleura may be involved.

Currently, 50% to 80% of individuals in occupational groups with exposures beginning more than 20 years earlier have been found to have abnormal X-rays. These include asbestos insulation workers (Selikoff et al. 1965), miners and millers (Nicholson, 1976b), and asbestos factory employees (Lewinsohn, 1972). In many circumstances, the disease progresses following cessation of exposure; in a group employed in an asbestos factory for various periods of time between 1941 and 1954, X-ray changes were observed years following exposure in individuals having exposures as short as one week (Personal communication, I.J. Selikoff).